The Burden of Infection-Associated and Common Cancers Among South Asians and Other Asian Subpopulations in the United States, 1999-2009

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Dedications

I dedicate this dissertation to my family, my parents and brother, who have always supported and encouraged me in all my endeavors. This work would not have been possible without them by my side.

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Abstract

The Burden of Infection-Associated and Common Cancers Among South Asians and Other Asian Subpopulations in the United States, 1999-2009

Neena Sarah George

Cancer surveillance systems often do not provide detailed estimates of disease among racial/ethnic minorities due to the use of combined racial groups such as Asian/Pacific Islander. The current cancer burden in the South Asian population in the U.S. is largely unknown due to the lack of studies that examine this group separately from other Asian/Pacific Islander populations. We utilized SEER data to examine differences in stage at diagnosis and survival of infection-associated (liver, stomach, and cervical) and common (breast) cancers among South Asians compared to other Asian subpopulations in the U.S. SEER-Medicare data were used to assess the association between primary care physician visits and these cancer outcomes among these groups. In our study of infection-associated cancers, it was found that South Asians had the highest proportion (48%) of late stage liver cancer cases compared to the other Asian subpopulations examined. When examining breast cancer outcomes among the Asian subpopulations, the highest risk for late stage diagnosis when compared to non-Hispanic whites was found among South Asians, with 3% (OR=0.97; 95% CI 0.81, 1.16) reduced risk for late stage diagnosis for this group. When examining those diagnosed at early-stage disease, South Asians had 39% significant reduced risk (95% CI 0.44, 0.84) of death when compared to non-Hispanic whites. Among those diagnosed with late-stage disease, this group had 20% reduced risk (95% CI 0.59, 1.09) of death when compared to non-Hispanic whites. Primary care visits were associated with decreased risk of late stage

diagnosis of breast cancer among both Asians and non-Hispanic whites. Asians in the highest quartile of total physician visits had 57% (OR=0.43; 95% CI 0.27, 0.70) decreased risk of late stage diagnosis compared to those in the lowest quartile. Our findings provide evidence for the need to examine Asian subpopulations as individual groups rather than using the aggregate racial/ethnic category known as Asian/PI. True heterogeneity in cancer outcomes exists within these separate groups and requires targeted interventions for specific subpopulations.

1. BACKGROUND AND LITERATURE REVIEW

Cancer is a significant cause for public health concern among Asian Americans in the U.S. This racial/ethnic population is the only one for which the number of deaths annually attributable to cancer exceeds that of heart disease. Though this group reports lower rates for major cancers, such as lung, colon, and prostate, they report high rates of cancers associated with infectious agents. These include cancers of the liver, stomach, and cervix [1].

The U.S. Census characterizes Asian Americans as those who originate from the Far East, Southeast Asia, and the Indian subcontinent. Those who originate from these countries are extremely diverse in terms of factors such as time since immigration to the U.S., languages spoken, socioeconomic status, and religion. These are all factors which may impact chronic health outcomes. These racial/ethnic groups have been found to differ in their outcomes for cancer and other chronic conditions [1]. In addition, cultural factors, such as diet and tobacco use, likely play a role in differing patterns of cancer incidence and survival [2]. Thus, combining all Asian-Americans into one category may mask significant differences related to incidence and survival that are inherent within the subpopulations [3].

Through the use of cancer surveillance systems such as state cancer registries, we are able to monitor temporal patterns of cancer incidence, mortality, and overall survival. The introduction of national comprehensive surveillance programs, such as the National Cancer Institute's (NCI) Surveillance, Epidemiology, and End Results (SEER) program

has enabled us to examine trends in cancer occurrence. However, these systems are often limited for detailed estimates of disease occurrence across many racial/ethnic minorities due to the use of combined racial/ethnic groups such as Asian/PI. The use of such combined categorizations of race obscures significant differences in cancer occurrence patterns among specific racial/ethnic groups, such as those of South Asian origin [4]. Though they are the third largest Asian subpopulation [3], South Asians comprise a racial/ethnic group residing in the U.S. whose cancer experience has not been well examined and documented in the literature [5]. Thus, in order to better understand and address the cancer burden on the South Asian population, this study will examine this racial/ethnic group separately from other Asian/PI populations.

Three infection-associated cancers which are common among those of Asian origin have been chosen for analysis in this study. These include cancers of the liver, stomach, and cervix. A common cancer which will be analyzed is breast cancer. Cancer of the breast has been chosen to represent a non-infection associated cancer for purposes of comparison. We would like to examine whether the same differences in stage at diagnosis and survival are seen for this cancer compared to the other infection-associated cancers. For example, the subpopulation that has been found to have the most advanced stage at diagnosis for liver cancer may not also have advanced stages of breast cancer. Thus, there may be a significant impact of a specific country of origin for an outcome among infection-associated cancers that is not also seen for breast cancer. Incidence rates of these cancers were examined by Miller et al in 2008 [4]. We aim to update and extend

these results by examining stage at diagnosis and survival of these cancers by Asian subpopulation.

1.1. Liver cancer

1.1.1. Epidemiology in the U.S.

The most common malignancy of the liver is known as hepatocellular carcinoma (HCC) [6]. Almost 90% of primary liver cancers diagnosed in the United States are classified as HCCs, with the remaining 10% classified as intrahepatic cholangiocarcinomas (ICC) [7]. Since the majority of primary liver cancers are HCCs, these two terms are often used interchangeably [8]. The incidence of HCC in the U.S. has been historically lower compared to other regions of the world, such as East Asia. However, it has been found that in recent years age-adjusted incidence rates have significantly increased and mortality rates have increased more rapidly compared to other leading cancers [7]. The overall age-adjusted incidence rates of HCC tripled between 1975 and 2005, increasing from 1.6 per 100,000 to 4.9 per 100,000. In addition, it was found that incidence was almost three times greater among men compared women during this time period. Asian/Pacific Islanders had the highest age-adjusted incidence rates between 1992 and 2005, followed by Hispanics, blacks, American Indians/Alaska Natives, and whites [7]. In the U.S. in 2013, liver cancer is expected to be the fifth leading cause of cancer mortality among men, accounting for 5% of cancer deaths and the ninth leading cause of cancer mortality among women, accounting for 2% of cancer deaths [9]. The 5-year survival rate is about 10% since most patients with HCC are diagnosed at advanced stages of disease and are only candidates for palliative care as treatment [7].

Chronic infections with hepatitis C virus (HCV) and hepatitis B virus (HBV) are the leading causes of HCC in the U.S. HCC accounted for almost 18,910 deaths in the U.S. in 2010, with at least half of these attributable to HCV infection. Recent analyses of mortality rates through 2004 have indicated a decrease in deaths associated with HBV and an increase in deaths associated with HCV. It is expected that between 2010 and 2019, there will be a 2-fold increase in HCV-associated deaths, leading to direct medical costs exceeding $6.7 billion. It is estimated that between 800,000 and 1.4 million persons in the U.S. currently have chronic HBV infections. Among those infected, almost 50% are of Asian descent. In addition, almost 3.2 million persons are living with chronic HCV infections [10].

It is believed that the true burden of chronic HBV infection in the U.S. is largely unknown due to the lack of routine screening and the absence of comprehensive surveillance programs for HBV. In addition, the majority of those with HBV infection in the U.S. are likely foreign-born immigrants, who are unaware of their HBV status. It has been found that only 0.1-0.2% of U.S.-born individuals are infected with chronic HBV. In 2009, it was estimated that the number of foreign-born individuals living in the U.S. with chronic HBV infection was 1.32 million (95% CI 1.04-1.61). The countries from which the largest number of infected individuals originated included China (12.3% of Chinese immigrants), Vietnam (12.5% of Vietnamese immigrants), and the Philippines (7.4% of Filipino immigrants). This underestimation of the burden of chronic HBV in the U.S. highlights the fact that about 60-70% of those who are infected are undiagnosed and only almost 50% of those who are diagnosed receive proper treatment. Cultural,

personal, economic, and environmental factors likely promote barriers which contribute to the high proportion of foreign-born individuals who are unaware of their infection status. The prevalence of chronic HBV in the U.S. is likely to increase due to ongoing immigration of foreign-born individuals from countries in Asia with intermediate and high endemicity [11].

1.1.2. Risk factors

1.1.2.1. Hepatitis B virus (HBV)

Chronic infection with HBV is the most common cause of HCC worldwide [12]. Almost 5% of the global population (350-400 million people) has a chronic HBV infection. Almost 75% of those infected are Asian [13]. More than 50% of HCC cases globally and 70-80% of cases in highly endemic areas are attributable to HBV infection. The relationship between HBV infection and HCC was reported first in 1975. Several mechanisms have been proposed in recent years to describe the role of HBV in HCC etiology. One such mechanism is HBV DNA integration into the host genome. Such integration would allow for persistence of the virus in the liver and induce genetic alterations. Indirect mechanisms, such as HBV causing chronic hepatic injury and hepatocyte regeneration, have also been proposed. The mechanism of chronic infection has been recognized as an important risk factor due to its accompanying biologic processes of liver cell necrosis, inflammation, fibrosis, and cytokine synthesis. Repeated necrosis of hepatocytes in the liver due to chronic infection leads to rapid regeneration which may cause accumulation of mutations. HBV-associated HCC occurs as a result of chronic inflammation and continuous regeneration of cells, usually occurring after 25-30

years of infection. Lifetime risk of HCC in an individual that is chronically infected is almost 10-25%. Those with chronic HBV infection and underlying liver cirrhosis have increased risk of HCC [12].

HBV infection acquired during childhood typically leads to chronic lifelong infection and is typical in areas where HBV is endemic. If infection is acquired during adulthood, the result will usually be symptomatic acute hepatitis and gradual clearance of the infection in most patients. In the U.S. where HBV prevalence is low, the majority of those with acute HBV infection are adults and chronic infection will persist in only about 1-5% of those who are newly infected. The incidence of acute HBV in the U.S. has decreased steadily by 80% between 1987 and 2004. This reduction in incidence is attributable to many factors such as universal vaccination of infants at birth and vaccination of previously unvaccinated adults at increased risk for the infection [14]. In areas of low HBV endemicity but large populations of Asian immigrants, such as the U.S., almost 70-80% of HBV-associated HCC cases will be of Asian origin [12].

As stated previously, Asian immigrants residing in the U.S. have a greater prevalence of HBV infection compared to non-Hispanic whites and other U.S.-born persons. It is the main factor that contributes to the disproportionately high incidence of liver cancer among those of Asian origin. Chronic HBV infection is prevalent among about 10% of those residing in eastern and southeastern Asia, as well as among immigrants from these regions [15]. It is estimated that 10% of Chinese-Americans are infected [16]. The prevalence in Vietnamese-Americans ranges from 7% to 14% [17]. The prevalence of HBV among Japanese-Americans, ranging from 0.6% to 1.1%, is fairly low compared to

other Asian subpopulations. Fairly high prevalence is found among Filipino-Americans ranging from 4.2% to 9% [18]. The prevalence among South Asians in the U.S. has not been thoroughly examined. However, it is estimated that prevalence among those of South Asian origin range from 2% to 2.6% [19].

1.1.2.2. Hepatitis C virus (HCV)

Almost 170 million people worldwide are chronically infected with HCV [20]. Recent trends of increased incidence of HCC in developed regions, such as North America and Europe, have been attributed to HCV infection. Many forms of biological evidence indicate a strong association between HCV and HCC. HCV RNA does not integrate into the host genome as found among those with HBV infections. However, it can be found in the serum, liver, and tumor tissues of patients diagnosed with HCC. HCV likely increases the risk for HCC through promotion of fibrosis and cirrhosis. In fact, the majority of HCV-associated HCC cases are among patients with underlying cirrhosis. Most cases of HCC occur after 25 to 30 years of chronic infection with HCV. This interval of time also reflects the time that is necessary for development of cirrhosis [21]. In addition, it has been reported that 5-10% of patients with HCV infection will develop cirrhosis after 10 years of infection. This likelihood is 10- to 20- fold greater than among those who are HBV infected [22].

In the U.S., HCV infections are the most common bloodborne infections. The most significant means of viral transmission is through exposure to the blood of an infected individual. Common modes of transmission include intravenous drug use and sexual

contact with an infected individual [23]. It is believed that the HCV epidemic in the U.S. began in the 1960s and peaked in the 1980s when risk factors for HCV transmission, such as injection drug use, needle sharing, transfusion of unscreened and contaminated blood, and unsafe sexual behaviors were rampant. Thus, the incidence of HCV-associated HCC is expected to increase as those infected with HCV develop cirrhosis and subsequently HCC [21]. Increasing incidence rates of liver cancer among Hispanics, whites, and blacks in the U.S. are attributed primarily to HCV infection [15]. Unlike HBV, effective vaccination against HCV is not yet available. This is due to factors such as the high propensity of HCV to induce persistent chronic infection and evidence that convalescent individuals can be re-infected following new exposure [22].

The prevalence of HCV infection ranges from ≤1% -2% in developed countries to 6% in countries such as Vietnam where the infection is endemic [24]. In the U.S., the prevalence is believed to be approximately 1.8% [23]. Studies of Asian-Americans have shown that rates of HCV prevalence reflect those of their countries of origin [24]. The prevalence of infection among Chinese is about 3.2% [25]. Fairly low prevalence rates of 0.4% and 0.49% have been reported among those of Filipino and Japanese origin, respectively. The prevalence of HCV among South Asians residing in the U.S. has not been examined thoroughly but is believed to range between 0.8% among Indians to 5.3% in Pakistanis [26]. The rate of HCV is especially high in Pakistan largely due to reuse of syringes and needles. The practice of re-selling used needles as new instruments in drug stores is common in certain areas resulting in widespread use of unsterilized and infected needles. One study reported that among 68% of injections that were administered in two different districts in Pakistan, only 54% used needles which were new and freshly opened [27].

1.1.2.3. Aflatoxin

Aflatoxin is a mycotoxin produced by fungi belonging to the *Aspergillus* species. Contamination by aflatoxin mainly occurs as a result of improper storage of cereals, peanuts, and vegetables [6]. It is estimated that approximately 4.5 billion people worldwide are at risk for aflatoxin exposure through dietary intake. Areas at the highest risk of exposure are tropical and subtropical regions where maize and peanuts are consumed regularly [28]. Numerous prospective studies have shown strong associations between aflatoxin exposure and subsequent liver cancer. Aflatoxins, especially aflatoxin B_1 (AFB_1), have therefore been confirmed to have a carcinogenic role in liver cancer etiology. In addition, they may also interact with HBV infection to cause cancer [6]. Several studies have found that aflatoxin exposure and HBV infection may have a synergistic effect to increase risk of HCC in areas where both are prevalent [28]. AFB_1 exposure is usually prevalent in regions where HBV infection is also prevalent [6]. These include areas of the developing world, such as Asia and Africa. A recent meta-analysis which reviewed studies conducted in China, Taiwan, and sub-Saharan Africa reported that the population attributable risk (PAR) of aflatoxin-related liver cancer was 17% overall and 21% in populations with high rates of HBV infection. Thus, reducing aflatoxin exposure to levels classified as non-detectable could possibly reduce HCC rates in high-risk areas by about 17% [28]. Though exposure to aflatoxins is controllable through proper food storage methods, the regions of the world where exposure is prevalent do not have adequate resources to implement such control measures. The majority of agricultural land in Asia and Africa is in areas where climates are favorable to *Aspergillus* growth. Maize and groundnuts, two staples of Asian and African diets, are

the most conducive to *Aspergillus* proliferation and contamination. Since those residing in these areas can not afford to consume a diet rich in other nutrients, these foods contribute greatly to daily intake and thus results in high exposure to aflatoxins [29].

1.1.2.4. Alcohol

Alcohol consumption is associated with an increased risk of liver cancer. There is no clear "safety threshold" for the effects exerted by alcohol on the liver. A meta-analysis examining this association found a dose-response relationship with 25, 50, and 100 grams of alcohol intake per day associated with relative risks of 1.19 (95% CI 1.12, 1.27), 1.40 (95% CI 1.25, 1.56), and 1.81 (95% CI 1.50, 2.19), respectively. The most probable biological mechanism through which alcohol exerts its effect is through the onset of liver cirrhosis [6]. Almost 90% of ingested alcohol is metabolized in the liver and alcohol metabolism is the main cause of liver damage [30]. Cirrhosis is likely the most significant risk factor for HCC in regions such as North America where there is low prevalence of other factors such as HBV and HCV infections and exposure to aflatoxins [6]. In the U.S., about 32% of HCC cases are attributable to chronic heavy alcohol use [31]. A Swedish cohort study found that among subjects diagnosed with both alcoholism and cirrhosis, the relative risk of liver cancer was 16.5 (95% CI 12.7, 21.2). Infection with HCV may accelerate the course of alcoholic liver disease and lead to the onset of HCC at younger ages among drinkers compared to non-drinkers [6]. Alcohol consumption among those with HCV infection increases HCC risk by approximately 2-fold compared to those with HCV infection and do not consume alcohol [31]. However, alcohol is associated with HCC, regardless of the presence of either HBV or HCV infection. It is likely that higher

levels of consumption are necessary for development of cancer when viral infection is absent [20]. Several studies have provided strong evidence to support the notion of synergism between HCV infection and alcohol in liver disease etiology. Among those with HCV-associated disease, those with HCC or cirrhosis reported higher alcohol intake compared to those at less advanced stages of disease. In addition, cohort studies conducted among those with HCV-associated liver disease have reported that consumption of alcohol increases the rate of disease progression of fibrosis and carcinogenesis of the liver [32].

1.1.2.5. Smoking

Tobacco smoking is believed to be associated with increased risk of liver cancer. A meta-analysis examining this association reported an odds ratio of 1.56 (95% CI 1.29, 1.87) among current smokers compared to never-smokers [6]. The biological mechanism through which smoking exerts its effect on HCC etiology remains unclear. Animal studies have shown that tobacco-associated carcinogens can initiate tumor formation in the liver and inactivate tumor suppressor genes [33]. Since smokers have been shown to consume more alcohol than non-smokers, and heavy alcohol consumption is a risk factor for liver cancer, it may confound the association between smoking and liver cancer. However, there are numerous studies that have adequately controlled for this confounding and have concluded that smoking is itself an independent risk factor. Such studies include those conducted among Chinese and Japanese women, who likely do not consume heavy amounts of alcohol. Large case-control and cohort studies from the U.S.

and Asia have found relative risks between smoking and HCC to range between 1.5 to 2.5 [34].

1.1.3. Rationale for analyses

Liver cancer remains to be one of the most significant health disparities between Asian Americans and non-Hispanic whites in the U.S. They are 2.7 times more likely to develop the disease and 2.4 times more likely to die as a result. Though the burden of liver cancer is relatively low in the U.S., it remains as the second most common cause of mortality attributable to cancer in Asian American men. Regardless of medical advances for other cancer sites, the 5-year survival rate for liver cancer is still below 10%. This highlights the need for increased prevention targeted towards the high-risk Asian American population [35].

Despite recent successes in reducing the incidence of acute and chronic HBV infections in children and adolescents in the U.S., chronic HBV infection remains an important public issue among Asian/Pacific Islander adults residing in the U.S. Almost 10% of this population is chronically infected with HBV in comparison to less than 0.5% of the overall U.S. population. It has been shown that if left untreated, chronic infection of HBV results in death due to liver failure or cancer in approximately 1 in 4 people. These outcomes are the cause of death in approximately 3000 to 5000 individuals annually in the U.S. The significant racial/ethnic disparity in burden of chronic HBV infection in the U.S. is largely due to the fact that 67% of the Asian/Pacific Islander population is foreign-born. Those that comprise this group are originally from countries where HBV

infection is endemic. In addition, most of these chronic infections were likely acquired before adulthood. Due to the high prevalence of chronic infection in this population, liver cancer incidence is more than 3-fold higher among males of Asian/Pacific Islander origin compared to white males. In addition, almost 60-80% of liver cancer cases in this population are due to infection with HBV [36].

It is likely that part of the racial/ethnic disparity in liver cancer is also due to undiagnosed chronic HBV infection. Since there usually are no apparent symptoms of chronic infection, those that are affected are unaware of their infection. It has been reported that almost 60% of those with HBV infection do not experience any symptoms. The lack of screening in high-risk populations from regions of high endemicity also contributes greatly to under-diagnosis of HBV. Screening rates as low as 8% have been reported among urban foreign-born Asian/Pacific Islander communities. Several personal and environmental factors likely contribute to this lack of screening and awareness of infection status, especially among foreign-born populations that are at high risk. These include lack of correct information about the disease, cultural beliefs regarding primary care and physician visits, and fear of stigmatization from their communities [37]. All of these factors, which are prevalent among Asian immigrants, likely contribute to late stage at diagnosis and subsequent poor prognosis of liver cancer among this group.

It has been reported that approximately 40,000 immigrants with chronic HBV infections enter the U.S. each year, with 50% of these individuals classified as Asian [36]. HBV

infection is prevalent in Asia and is thus the most common cause of liver cancer in this region. Over 80% of liver cancer cases globally occur in developing countries and China alone accounts for more than 55% of total cases. The age-adjusted incidence rate of liver cancer in California was reported to be 23.3 per 100,000 among Chinese males compared to 6.8 per 100,000 among non-Hispanic white males. The rates for other Asian subpopulations such as Japanese and Filipino males were similarly increased compared to non-Hispanic white males at 9.3 and 16.8 per 100,000 respectively [1]. Though the South Asian population is rapidly growing in the U.S, the liver cancer burden of this group has not been adequately examined. A study conducted in California found that this group had increased incidence rates compared to non-Hispanic whites. The incidence rate among South Asian males was found to be 10.4 per 100,000 compared to 6.3 per 100,000 among non-Hispanic white males [38].

As seen in T**able 1-1**, the majority of studies examining liver cancer incidence among Asian subpopulations in the U.S. have been restricted to California since it has the largest Asian population in the country and its comprehensive state cancer registry which collects detailed information regarding health status among ethnic minority groups [1]. In order to better understand the burden of liver cancer among Asian subpopulations in the U.S, it is necessary to examine stage at diagnosis and survival in the country as a whole. This will allow for better prevention and management efforts, such as educating this population about HBV screening and increasing vaccination efforts among adults who were not previously vaccinated as children.

1.2. Stomach cancer

1.2.1. Epidemiology in the U.S.

In 2013, it is expected that 21,600 new cases of stomach cancer will be diagnosed in the U.S., while 10,990 deaths will be attributed to the disease [9]. It currently ranks 14th among the most incident malignancies in the U.S [43]. Stomach cancer incidence and mortality rates are twice as high among Asian/Pacific Islander populations in the U.S., compared to whites. This is likely attributable to the increased prevalence of chronic infection with *Helicobacter pylori* (*H. pylori*) in these populations. Stomach cancer is also more commonly diagnosed in males compared to females. Among Asian/Pacific Islanders, the incidence rate was found to be 16.1 per 100,000 among males and 9.3 per 100,000 among females. Among whites, the incidence rate was found to be 8.4 per 100,000 among males and 4.0 per 100,000 among females. Over the past decade (2000-2009), some of the largest declines in annual mortality rates have been for cancers of the stomach (3.1%) [9]. Few cases of gastric cancer are diagnosed at early stages of disease in the U.S. Thus, the 5-year survival rate is relatively low at less than 20%. It has been reported that gastric cancers diagnosed among those of Asian origin carry a more favorable prognosis compared to non-Asians, suggesting that host-related factors also likely play a role in prognosis [44].

Almost 90% of gastric tumors are adenocarcinomas of two main histologic subtypes: well-differentiated (intestinal type) and undifferentiated (diffuse type). Intestinal type tumors are more common in high-risk regions, such as East Asia, Eastern Europe, and Central and South America. Diffuse type tumors follow a more uniform geographic

distribution. It is believed that decreasing incidence of intestinal type adenocarcinomas accounts for the majority of the recent declining trend of gastric cancers worldwide [44]. Stomach cancers are often further classified into two distinct entities: proximal (cardia) and distant (non-cardia) tumors [43]. Though a decreasing trend for distal tumors has been observed, incidence of proximal tumors has been increasing, especially among men. Proximal malignancies now account for almost half of gastric cancers among males in the U.S [44].

A recent study examining cancer incidence and mortality among Asian-American immigrants reported that stomach cancer was among the most common cancers in these groups. Incidence rates were especially high among Korean and Japanese men at 55.0 and 29.3 per 100,000, respectively [4]. This is expected since Korea and Japan have reported the highest rates of stomach cancer in the world [44]. Stomach cancers were also among the top four causes of cancer mortality among the majority of Asian groups examined. Previous studies conducted among immigrant populations have suggested early exposure to *H. pylori* and dietary factors likely play a role in stomach cancer incidence among those of Asian origin [4]. The unusually high rates of stomach cancer found in Korea are likely due to traditional dietary patterns which include frequent intake of foods high in salt and nitrites or nitrates [1].

1.2.2. Risk factors

1.2.2.1. Helicobacter pylori (*H. pylori*)

H. pylori, a gram-negative spiral bacterium known to infect nearly half of the global population, is the most well-known risk factor for stomach cancer [45]. *H. pylori* have the ability to invade and colonize the stomach and subsequently engage in direct interactions with gastric epithelial cells [46]. However, only a small percentage of those with the infection will develop the disease [45]. Regions with high rates of stomach cancer will typically also have increased prevalence of *H. pylori* infection. The association between *H. pylori* infection and increased risk of gastric cancer has been well established by previous studies. An increased risk of developing adenocarcinoma up to 6-fold has been reported for infected patients [46]. It was classified as a group 1 carcinogen by the International Agency for Research on Cancer in 1994. The biological mechanism through which infection triggers carcinogenesis involves a progressive sequence of events as follows: (1) gastric lesions resulting from chronic gastritis, (2) gastric atrophy, (3) intestinal metaplasia, (4) dysplasia, and (5) gastric adenocarcinoma [44].

In Asia, there is widespread geographic variation in seroprevalence rates of *H. pylori* infection. In addition, though the incidence of stomach cancer largely reflects seroprevalence rates of infection, there are groups with high seroprevalence that also have low rates of cancer. Within the Asian-Pacific region, there is considerable variation in *H. pylori* infection between countries and also among specific communities within countries. In Bangladesh the seroprevalence of infection was reported as 92%, while the overall rate in India was 79%. However, India is classified as a low-risk region for

gastric cancer where the age-standardized incidence rate is about 5.7 per 100,000. In contrast, high-risk regions for gastric cancer (Japan, China, Korea) where the seroprevalence ranges from 39.3% to 59.6% report age-standardized incidence rates ranging from 41.4 to 69.7 per 100,000. This paradox is referred to as the "Asian Enigma" and is likely attributable to host genetic factors and other environmental factors such as diet and smoking [47].

In developed countries such as the U.S., the prevalence of *H. pylori* infection varies according to age, ethnicity, and socioeconomic status. In contrast, prevalence in developing countries is less variable and less dependent on age and socioeconomic status. Consequently, prevalence of infection in developed countries is higher among immigrants compared to native-born individuals. Most immigrants in the U.S. originate from countries where *H. pylori* infection is prevalent among young adult populations. A study conducted in New York City found that seroprevalence of infection among East Asian immigrants was greater than 70% [48]. The prevalence of *H. pylori* infection in the U.S. is reported to be less than 20% among those 20 years of age and 50% among those 50 years of age. The prevalence of infection in Japan is also less than 20% at 20 years. However, it increases to 80% among those over 40 years. In Korea, 90% of adults over age 20 years who are reported to be asymptomatic are infected. The drastic increase in prevalence with increasing age observed in these countries is mostly due to an apparent cohort effect, rather than older age at infection since *H. pylori* is mostly acquired during childhood by oral ingestion. The likelihood of infection is associated with lifestyle and living conditions during childhood such as overcrowding and poor sanitation [44].

1.2.2.2. Diet

Salt intake has been shown to be a risk factor for gastritis and amplify the effects of gastric carcinogens [49]. A recent meta-analysis of prospective studies examining the association between salt intake and stomach cancer risk reported that "high" (RR=1.68; 95% CI 1.17, 2.41) and "moderately high" (RR=1.41; 95% CI 1.03, 1.93) intake were both associated with increased risk compared with "low" intake [50]. Mucosal damage caused by salt intake also likely increases the risk for persistent infection with *H. pylori* [49]. High consumption of salt-preserved foods and nitrosamines, such as those present in smoked fish and pickled vegetables, also likely increase the risk stomach cancer. Geographic variation in stomach cancer mortality rates has been shown to correlate with levels of daily salt consumption. In many developing countries, salting is used as a means of food preservation. The decline of stomach cancer in developed nations, such as the U.S., is attributed to the widespread use of refrigeration as the common method of food storage. It has been hypothesized that *H. pylori* infection acts synergistically with dietary factors to promote carcinogenesis [51].

Fruit and vegetable consumption has been shown to protect against stomach cancer risk. A large prospective study reported that intake of 2-5 daily servings of fruits and vegetables resulted in 44% reduced risk of cancer (HR= 0.56; 95% CI 0.34, 0.93) when compared to less than 1 daily serving [49]. Anticarcinogenic components of these foods, such as vitamins, carotenoids, and flavonoids, likely play a role in the observed protective effects through processes such as modulation of DNA methylation, protection from DNA damage, and promotion of apoptosis [52].

1.2.2.3. Alcohol

Though the association between alcohol consumption and stomach cancer risk has been examined in numerous studies, results remain inconsistent [53]. Recently, four large prospective studies concluded that there was insufficient evidence to support the association between total alcohol consumption and stomach cancer risk [54]. When this association was examined in the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort, it was found that heavy alcohol consumption (≥60 g/d) was positively associated with gastric cancer risk (HR=1.65; 95% CI 1.06, 2.58) when compared to very light consumption (0.1-4.9 g/d). In addition to ingestion of the nitrosamine NDMA, heavy alcohol consumption also increases exposure to ethanol and its major metabolite acetaldehyde, a known carcinogen. Acetaldehyde has been found to induce DNA lesions and bind to enzymes which are involved in DNA repair and antioxidant protection. The potential mechanism through which alcohol exerts its effect on stomach cancer risk is likely through the combined effects of acetaldehyde and nitrosamines in the gastric mucosa [53].

1.2.2.4. Smoking

Smoking has been examined as a risk factor for stomach cancer risk in numerous studies. In 2002, the International Agency for Research on Cancer reported that there was "sufficient" evidence to support a causal relationship as a result of moderately increased risk that was reported in both cohort and case-control studies. A recent prospective study conducted in Shanghai, China concluded that ever smokers were at increased risk of stomach cancer (HR=1.59; 95% CI 1.27, 1.99) compared with non-smokers after adjustment for confounders, such as alcohol intake. The statistically significant positive

association reported in this high-risk population between smoking and stomach cancer risk among non-drinkers suggested an independent role of tobacco use in the risk for stomach cancer. The biological mechanism through which smoking leads to increased stomach cancer risk is not well understood. However, it has been shown that tobacco smoke contains more than 60 known carcinogens. Thus, nitrosamines and other nitroso compounds in cigarette smoke are likely involved in gastric carcinogenesis. In addition, it has also been shown that smoking is associated with increased frequency of progression from normal gastric mucosa to precancerous lesions [55].

1.2.3. Rationale for analyses

Asian Americans are the only major racial/ethnic group in the U.S. that experiences more annual deaths due to cancer than heart disease. They are at higher risk for tumors associated with infectious agents, such as stomach cancer. Incidence rates for stomach cancer among certain subpopulations of Asian-American men have been reported as 6-fold higher compared to non-Hispanic white men. A study conducted in California reported that the incidence rate for Korean men was approximately 54.6 per 100,000, while the rate for non-Hispanic white men was 9.5 per 100,000. Mortality attributable to stomach cancer was also greatest among Korean males (35.2 per 100,000) and females (13.9 per 100,000) compared to other racial/ethnic groups [1].

It has been observed that Asian populations with more recent immigration histories to the U.S., such as Koreans and Vietnamese, experience a greater burden of cancers that are

usually not found at high rates in developed countries. The unusually high rates of stomach cancer found among Korean-Americans are one such example of this trend [1]. However, despite higher incidence of gastric cancer, Asian countries consistently report more favorable outcomes related to disease compared to Western countries. This can be seen when examining 5-year survival in Japan (40-60%) compared to the U.S. and Europe (15-20%). A potential reason for these variations in survival between regions likely includes inherent differences in tumor biology. In Western countries, proximal (cardia) gastric tumors are more common while the majority of tumors found in Asia are distal (non-cardia) tumors [56].

As described previously, the presence of the "Asian enigma" does not allow for accurate estimates of stomach cancer burden if various Asian populations are combined to create one group known as Asian/Pacific Islander. Rates of *H. pylori* infection and subsequent gastric cancer rates vary greatly among the different Asian regions. Thus, it is necessary to examine the role of race/ethnicity on gastric cancer outcomes in order to tailor interventions to those at greatest risk of unfavorable outcomes. To date, the national burden of stomach cancer in Asian subpopulations has not been examined extensively in the U.S. As seen in T**able1-2**, gastric cancer incidence has not been examined thoroughly using all available national SEER registries. Kamineni et al examined the burden of gastric cancer among U.S.-born and foreign-born Asian immigrants in California between 1973 and 1986 [57]. We aim to update and extend these results to include additional subpopulations and all available nationwide SEER registries to

describe current differences in stage at diagnosis and survival of stomach cancer in the U.S.

1.3. Cervical cancer

1.3.1. Epidemiology in the U.S.

In 2013, it is estimated that 12,340 new cases of cervical cancer will be diagnosed in the U.S. In addition, it will be associated with 4,030 deaths [9]. It is currently the 13th most common cancer among women in the U.S. Rates of incidence and mortality have decreased by more than 75% since the 1940s due to the introduction and implementation of screening and treatment of pre-cancerous lesions in the cervix. The age-adjusted incidence has decreased from 14.8 per 100,000 in 1975 to 6.6 per 100,000 in 2008. Though the overall incidence and mortality rates of cervical cancer have decreased in recent years, disparities in burden of disease persists. More than 60% of cases in the U.S. are diagnosed in underprivileged groups including racial/ethnic minorities and women living in poverty who are less likely to have access to screening and treatment [59]. The highest incidence rates are reported for Hispanic women (14.4 per 100,000), while the lowest rates are reported for Asian/Pacific Islander women (8.8 per 100,000) [60]. Fortunately, more than half of all cervical cancers are usually diagnosed at the localized stage [61].

The introduction of the Papanicolaou (Pap) test in the 1940s led to the widespread decrease in cervical cancer incidence in the U.S. and other developed countries. Since most cervical carcinomas are classified as squamous cell carcinomas (SCC), the decline in incidence and mortality can be attributed largely to the ability of screening tests to detect pre-invasive SCC. However rates of the rarer subtype, cervical adenocarcinoma (AC), have been on the rise in developed nations in North America and Europe as well as

developing nations such as India and Japan. This increase in incidence may be due to improved methods of screening which now allow for increased recognition and detection of AC lesions that were previously undetected and classified as unknown histology in earlier decades [62]. It is known that the Pap test can more readily detect squamous cell types rather than glandular cell types which give rise to ACs. This is due to the anatomy of the cervix since endocervical tissue which contains glandular cells is more difficult to sample during a Pap test compared to the squamous epithelium of the ectocervix. This is also the cause of late stage presentation and diagnosis that is often reported for ACs [63].

Several studies have documented lower rates of cancer screening overall among Asian Americans. While disparities in screening between non-Hispanic whites, Latinos, and blacks in the U.S. can be explained by socioeconomic status and access to care, this is not the case for Asian Americans. For this population, the most significant factors that play a role in reduced rates of screening are nativity and language. Most Asians in the U.S. are foreign-born and migrate from countries where limited attention is given to chronic disease prevention and where population-based screening services are not available. A study examining screening behaviors among Chinese, Filipino, Vietnamese, Korean, Japanese, South Asian, and Cambodian populations in the U.S. found that foreign-born status and living in the U.S. fewer years were both significantly and independently associated with lower rates of cervical cancer screening compared to those classified as U.S.-born. Foreign-born Asians were also more than twice as likely as U.S.-born non-Hispanic whites to report that the most important factor contributing to not undergoing screening tests was because “they haven’t had problems or symptoms.” Thus, certain

subpopulations of Asian women still remain at increased risk for cervical cancer due to lack of screening. It is the leading type of cancer among Korean, Vietnamese, and Cambodian women, while high mortality rates are found among Chinese women. Significant disparities remain in cervical cancer screening, regardless of insurance, access to care, and socioeconomic status [64].

1.3.2. Risk factors

1.3.2.1. Human papillomavirus (HPV)

Human papillomavirus (HPV) has long been identified as a necessary cause of cervical cancer. The natural history of cervical cancer begins by acquiring a sexually transmitted carcinogenic HPV infection [65]. Virtually all cases are attributable to persistent infection with one of almost 15 types of oncogenic genotypes of HPV. HPV16 and HPV18 are the two most common forms of HPV and responsible for 70% of all cervical cancers and almost 50% of cervical intraepithelial neoplasia grade 3 (CIN3) [66]. Almost half of all HPV infections are undetectable within 6-12 months and greater than 90% of infections clear within a few years [67]. Knowledge of HPV's role in the etiology of cervical cancer has led to preventive methods, such as vaccines and HPV-based screening, that focus on early stages of infection [65].

Cervical cancer develops through progression of four stages of carcinogenesis: HPV infection, viral persistence rather than clearance, development of high-grade precursor lesion, and invasion. It is known that most sexually active women are infected with at least one form of HPV during their lifetime. In addition, millions of women are diagnosed annually with some form of abnormality when screened for cervical lesions.

However, almost all abnormalities are cleared without need for treatment. The majority of cervical HPV infections are cleared or suppressed within 1-2 years after exposure by cell-mediated immunity mechanisms. Longer persistence of HPV leads to decreased probability of clearance and increased likelihood of pre-cancer diagnosis [66]. About 10% of carcinogenic infections that persist for several years are strongly associated with an increased risk of pre-cancer. In the pre-cancer stage, undifferentiated cells with fixed genetic abnormalities replace the majority of the cervical epithelium. The interval between infection and first evidence of a pre-cancerous lesion is usually about five years. Average age at diagnosis of pre-cancer is usually between 25 and 35 years, dependent upon age at first intercourse and the intensity of screening within the population. HPV16 is the most carcinogenic genotype, with an absolute risk of pre-cancer diagnosis at almost 40% following 3-5 years of persistent infection. The age range at which risk of invasive cervical cancer peaks in unscreened populations is usually between 35 and 55 years. This peak in incidence occurs much earlier than for most other adult cancers. One reason for this early age at diagnosis is likely that cervical cancers occur as a result of HPV infections acquired in late adolescence and early adulthood. In addition, the interval between infection and development of pre-cancer is relatively short. HPV16, 18, and 45 are found in more cancers and pre-cancers compared to other genotypes. An important distinction between infection and pre-cancer is integration of HPV DNA into the host genome, since integration is associated with invasive cancer. Continuous transcriptional activity from HPV oncogenes is necessary for maintenance of the cancer [66].

In the U.S., HPV is believed to be the most sexually transmitted infection. Prevalence of the infection is usually reported to be the highest among young persons within a few years following first sexual intercourse. According to the NHANES 2003-2004, HPV prevalence (44.8%) was highest among females aged 20 to 24 years. In addition, there was a statistically significant trend for increasing prevalence for each year of age between 14 and 24 years. The overall HPV prevalence among females aged 14 to 59 years was 26.8% [68].

The prevalence of HPV infection among Asian subpopulations in the U.S. has not been extensively studied. However, geographical variation in the prevalence of HPV genotypes has been examined. It has been reported that though high-risk HPV types 52 and 58 are not commonly found in most populations, they are common among Chinese and Japanese women. A study in Vietnam reported that the prevalence of HPV infection among women aged 25 years and older is about 7.6% to 10.9%. This high prevalence is one explanation for the significantly high incidence of cervical cancer reported among Vietnamese women in the U.S. who have reported low rates of Pap test screening [69]. A recent population-based study conducted in China found the prevalence of HPV among the general population to be about 18.4% [70]. Relatively high rates of HPV infection (>10%) are also found among women of South Asian origin [71].

1.3.2.2. Oral contraceptive use

The likelihood of a woman infected with HPV subsequently progressing to persistent infection or cervical cancer may be affected by other factors, such as use of hormonal

contraceptives. A systematic review of this association concluded that the relative risk of cervical cancer increased with increasing duration of use of oral contraceptives among women who were HPV-positive. The relative risks associated with duration of use less than 5 years, 5-9 years, and 10 years or more were as follows: 0.90 (95% CI 0.70, 1.20), 1.30 (95% CI 1.00, 1.90), and 2.50 (95% CI 1.60, 3.90) respectively [72]. The biological mechanisms associated with contraceptive use through which infection progresses to carcinogenesis remain unclear. It has been hypothesized that contraceptive use may affect the likelihood of clearance or persistence of HPV infection. It may also affect the regression or progression of pre-neoplastic and neoplastic lesions [73].

1.3.2.3. Parity

Multiparity has been associated with increased cervical cancer risk for several decades. While it has been argued that other reproductive characteristics may affect this relationship, an independent role in cancer risk has been observed for multiparity while also controlling for potential confounders that indicate sexual habits and behaviors. A pooled analysis investigating this association found that high parity increased the risk of squamous cell carcinoma of the cervix among women classified as HPV-positive. The odds ratio associated with seven or more full-term pregnancies and risk of cervical cancer was 3.80 (95% CI 2.70, 5.50) compared with nulliparous women. When comparing women with seven or more full-term pregnancies to those who had one or two full-term pregnancies, the odds ratio was found to be 2.30 (95% CI 1.60, 3.20). Serum concentrations of progesterone and estrogen increase steadily during pregnancy and reach their highest concentrations during the last weeks before delivery. These hormonal

variations are likely a cause for alterations in the transformation zone of the cervix, where most cancerous lesions are thought to arise. Thus, the role of high parity on cervical cancer risk may be through its effect on the transformation zone by causing it to be vulnerable to direct exposure from HPV infection [74].

1.3.2.4. Smoking

Several studies have found an association between smoking and increased risk of cervical cancer and its immediate precursor, cervical intraepithelial neoplasia grade 3 (CIN3). Biological plausibility that provides support for this association includes the presence of nicotine derived carcinogens found in cervical mucus following smoking. A study examining the role of smoking as a risk factor for CIN3 among HPV-positive women found that current smokers (OR=1.70; 95% CI 1.40, 2.10) and past smokers (OR=1.70; 95% CI 1.20, 2.40) were at increased risk for CIN3 or cancer compared to non-smokers. In addition, greater intensity of smoking and duration strengthened the magnitude of this association. It is likely that smoking exerts an effect on the interaction between HPV infection and biological processes in the host through a mechanism which increases the likelihood of pre-malignant change in the cervix. Since the presence of carcinogenic metabolites produced by smoking has been detected in cervical secretions, smoking may increase the risk for CIN3 by promoting viral persistence or through producing genomic damage through genotoxins [75].

1.3.3. Rationale for analyses

Major health disparities in cervical cancer incidence and mortality have been documented among Asian-American women. Women of Vietnamese origin have incidence rates that are up to five times higher than non-Hispanic white women in the U.S. [76]. A study examining the burden of cervical cancer among Asian populations in California found that it greatly varies among subpopulations. Vietnamese and Korean women were found to have greater incidence rates compared to non-Hispanic whites. In addition, it was found that the rates found among Asian women in the U.S. broadly mirrored rates found in their countries of origin. The exception to this general finding was among South Asian women. Though relatively high cervical cancer incidence rates are found in India, the South Asians living in California had the lowest rates compared to other subpopulations. This difference in rates is likely attributable to the high level of education found among South Asians in the U.S. compared to other Asian populations [77]. Studies conducted among Asian-American women have shown that this group lacks proper knowledge regarding cervical cancer risk and testing. In addition, cultural attitudes towards sexual activity may also contribute to the disparity and lower rates of screening [76].

Though great advances in early detection of cervical cancer have been achieved in the U.S. through improved screening practices, the burden of disease remains disproportionately high among immigrant and minority women. It has been estimated that 50% of those diagnosed with cervical cancer have never been screened. More than half of the total deaths due to cervical cancer in the U.S. occur among foreign-born women. In addition to cultural and socioeconomic barriers to proper screening, these

women also experience less timely contact overall with the health care system. Despite the potential to reduce disparities in cervical cancer outcomes through widespread HPV vaccine coverage, these sociocultural barriers prevent proper vaccination among immigrant women and adolescent girls [78]. Although factors contributing to low prevalence of screening have been identified among Asian immigrant women, few programs have been developed to increase screening uptake in this population. The majority of interventions have targeted Vietnamese-American women and have been community-based [79].

As stated previously, distinct differences in overall incidence of cervical cancer have been found among Asian subpopulations residing in California. Evaluation of this group as an aggregate will therefore mask true variations that are associated with known and unknown socioeconomic, cultural, and behavioral differences [80]. As shown in **Table 1-3**, the burden of cervical cancer in these individual subpopulations has not been extensively examined using all of the available registries in SEER. Such differences among racial/ethnic groups may suggest varying ages at onset of infection and may require changes in recommendations for immunizations and screening in certain populations. Thus, we aim to examine subpopulations of the Asian population to describe current differences in stage at diagnosis and survival of cervical cancer in the U.S. Assessment of these differences will allow us to determine which specific subpopulations are in need of targeted interventions to reduce the burden of this disease.

1.4. Breast cancer

1.4.1 Epidemiology in the U.S.

Breast cancer is the most common cancer and the second leading cause of death attributable to cancer among women in the United States [9]. There are currently approximately three million women in the U.S. who have been diagnosed with invasive breast cancer [81]. It has been estimated that breast cancer will account for about 29% of new cancer cases diagnosed among women in 2013. This amounts to approximately 232,340 incident cases. In addition, breast cancer is the second leading cause of cancer mortality among women and accounts for about 14% of deaths [9]. The median age of diagnosis has been reported to be 61 years. When examining age at diagnosis, 20% of cases occur among those younger than 50 years and 60% of cases occur among those 65 years and older. Diagnosis occurs at a localized stage for 60% of cases [81].

In 2010, breast cancer was reported as the cancer site with the highest cost of care, with almost $16.5 billion in medical expenditures. It is projected that this cost will increase 32% by 2020 [82]. In elderly populations, the cost of breast cancer care amounts to $1,923 in average monthly expenditure. Due to longer than usual survival compared to other cancer sites, patients diagnosed with breast cancer face higher costs during the time between initial diagnosis and the last year of life [83].

Historically, trends in breast cancer incidence can be summarized as follows: stable increase from 1940s to 1979, steep increase from 1980 to 1999, decrease from 2000 to 2003, and relatively stable rates after 2003 [84]. The increase in incidence reported in the

1980s was likely attributable to the introduction of mammography screening. In addition, changes in reproductive behaviors were also occurring during this time, such as delayed pregnancy and having fewer children. Use of menopausal hormones likely contributed to the increase in incidence in the late 1990s. The decline in rates found in the early 2000s was likely due to decreased use of menopausal hormones following the publication of results from the Women's Health Initiative reporting the association between these hormones and increased risk of breast cancer [85]. Unfortunately, incidence rates did not continue to decrease after 2003. Several factors may contribute to this apparent stabilization of incidence. One possible explanation may be the relatively stable rates of mammography screenings that have been conducted since 2000 [86]. When examining breast cancer mortality rates, increasing trends were observed between 1975 and 1990. Rates decreased by about 2.2% per year between 1990 and 2007. This decrease in mortality rates was greater among women younger than 50 years compared to those 50 years or older. The decline in mortality rates was largely due to improvements in both early detection and treatment [85].

1.4.2. Risk factors

1.4.2.1. Endogenous sex hormones

Estrogen and progesterone are sex hormones produced by the ovaries. Cumulative exposures to these hormones through various reproductive processes contribute breast carcinogenesis through their ability to stimulate cell proliferation. The likelihood of genetic mutations is increased through the effects of estrogen which include stimulating ductal growth and increasing rates of cell proliferation. Progesterone also stimulates cell

proliferation. Cumulative exposure to circulating levels of estrogen and progesterone during a woman's reproductive years has the greatest impact on breast cancer risk. Proliferation rates of breast epithelial cells are high during the luteal phase of a woman's menstrual cycle when the circulating levels of estrogen and progesterone are relatively high. However, breast cell proliferation is relatively low after menopause when estrogen levels are low and progesterone is absent [87].

1.4.2.2. Age at menarche

Early age at menarche has been established as risk factor for breast cancer. The risk of breast cancer decreases by 10% -20% with each additional year delay in the onset of menarche. In addition to age at onset of menarche, the time at which menstrual cycles become regular is also associated with risk. It has been found that breast cancer risk is doubled for those women who have regular cycles within 1 year of their first menstrual period compared to those who only have regular cycles after five years or longer. In addition, those with early age at menarche at age 12 years or younger who had established regular cycles within the first year of onset of their menstrual period have almost four times greater risk compared to those with age at menarche at age 13 years or later and longer duration of time with irregular cycles [87]. Reproductive processes that occur during the menstrual cycle reflect the underlying levels of circulating estrogen and progesterone. As a consequence, a shorter cycle length indicates a longer luteal phase during which proliferation of breast epithelial cells and circulating estrogen and progesterone are at their highest levels. Thus, due to higher rates of cell division, a shorter cycle length infers higher breast cancer risk [88].

1.4.2.3. Parity and age at first full-term pregnancy

Parity and early age at first full-term pregnancy are two of the earliest known protective factors for breast cancer. One early study found that the breast cancer risk for single and nulliparous married women was about 1.4 times the risk for parous married women. On average, women who have experienced at least one full-term pregnancy have about 25% reduced risk compared to nulliparous women [89]. In addition, women who had their first birth at age 20 years or younger had about half the risk compared to those women whose first birth occurred at age 30 years or older [87]. It has been proposed that the protective effect of early age at first full-term pregnancy may be due to the terminal differentiation of mammary gland epithelium that is induced through pregnancy. This differentiation reduces the likelihood of formation of precancerous lesions in the breast [90]. Increasing parity continues to reduce risk through the extended differentiation that is induced by repeated pregnancy. Older age at first pregnancy likely infers greater risk due to an increased length of time when the breasts are susceptible to carcinogens attributed to the presence of undifferentiated cells [91].

1.4.2.4. Breastfeeding

Breastfeeding has been shown to be associated with decreased breast cancer risk. Substantial risk reductions have been found for parous pre-menopausal and post-menopausal women who reported breastfeeding for longer than 15 months. Compared to those who never breastfed, a 35% reduction in risk was found for pre-menopausal women and 30% reduction in risk was found for post-menopausal women [87]. The U.S. Cancer and Steroid Hormone Study which examined the association between breastfeeding and

breast cancer risk found that those who reported breastfeeding for at least 25 months had 33% reduced risk compared to those who never breastfed after controlling for parity and age at first full-term pregnancy [89]. Breastfeeding is thought to infer its protective effect through causing a reduction in a woman's cumulative number of menstrual cycles. There is a significant delay in the return to experiencing regular cycles following a completed pregnancy [87]. The protective effect attributable to breastfeeding is likely stronger in younger women compared to older women [89].

1.4.2.5. Age at menopause

The duration of time between onset of menstrual cycles and menopause represents a woman's cumulative lifetime exposure to substantial levels of reproductive hormones. Thus, after menopause the circulating levels of these hormones are significantly lower. These reproductive processes also have an effect on the rate of breast cell proliferation and accumulation of damage to DNA [92]. Breast cancer incidence rates have been shown to plateau or increase more slowly following menopause [87]. The protective effect of menopause can often be seen by the slower rate of increase in incidence at around age 50 years [89]. Late age at menopause has consistently been shown to be associated with increased breast cancer risk. Those who experience early menopause have a shorter duration of menstrual cycles and less exposure to the hormones associated with them. The risk of breast cancer is about two times greater for women whose last menstrual period occurs at age 55 years or later compared to those who experience their last period at age 45 years or younger [87]. Risk has been found to increase by approximately 3% for each year that menopause is delayed. Due to the protection conferred by reaching

menopause, pre-menopausal women are at greater risk compared to women of the same age who are post-menopausal [89].

1.4.2.6. Oral contraceptives

It was originally believed that use of oral contraceptives increased breast cancer risk due to the hormones that they contained. It was thought that provided the body with higher levels of estrogen and progesterone than would have been produced during a normal ovulatory cycle, especially if use began at an early age. However, a re-analysis of data collected from 54 different studies conducted by the Collaborative Group on Hormonal Factors in Breast Cancer reported that recent oral contraceptive use rather than long duration of use contributed more to breast cancer risk [87]. There is almost 25% increased risk in current users of combined oral contraceptives. However, this risk decreases after cessation of use. A significant increased risk is no longer evident 10 or more years following cessation. It has also been found that use of combined oral contraceptives is associated more with localized tumors rather than those that have spread to other organs beyond the breast. This finding suggests that the increased risk found among recent users may in part be attributable to increased screening practices [89].

1.4.2.7. Post-menopausal hormones

Use of hormonal therapy for treatment of menopausal symptoms is often initiated at a time when the underlying for breast cancer is relatively high [89]. Several studies examining large cohorts of women who have reported prolonged use of estrogen replacement therapy for more than 10 year periods have found increased breast cancer risk. Risk has been reported to increase by about 3% per year of use. Combined hormone replacement therapies which include progestin in addition to estrogen increase risk substantially through enhancing the proliferative effects of estrogen. When progestin is added to create a combined therapy, the increase in risk resulting from five years of use changes from 10% to 30% [87]. The results of the Women's Health Initiative study published in 2002 shed light on the risks associated with hormone replacement therapy. An increased breast cancer risk was found among subjects in the combined therapy arm of this placebo-controlled trial. Those in the treatment arm with combined estrogen and progesterone had 25% greater risk of invasive breast cancers compared to those in the placebo arm [93]. Similar findings were reported in the Million Women Study conducted in the United Kingdom [94]. These findings largely contributed to the widespread cessation of hormone replacement therapy and the subsequent decrease in overall breast cancer incidence rates [95].

1.4.2.8. Diet

There have been inconsistencies across studies regarding the effect of dietary intake on breast cancer risk. The Women's Health Initiative Dietary Modification Trial reported that breast cancer incidence was 9% lower in the low fat intake intervention group

compared to the control group. The European Prospective Investigation into Cancer and Nutrition reported a weak positive association between saturated fat intake and risk. Despite inconsistencies across studies, there is biological plausibility to support an association between dietary intake and breast cancer risk. One such hypothesis is that increased fat intake may increase the concentration of endogenous estrogen. Several intervention studies have reported lower concentrations and bioavailability of serum sex hormones among those with lower fat intake. In addition, Consumption of saturated fat may be associated with increased risk through having adverse effects on insulin resistance. Studies have reported associations between plasma concentrations of insulin, C peptide, and insulin growth factor-I and breast cancer risk [96]. Inconsistencies in results have also been found for studies examining the association between fruit and vegetable intake and breast cancer risk. There are plausible biological mechanisms to support this relationship. Several fruits and vegetables contain substantial amounts of protective factors such as fiber, antioxidant vitamins, minerals, and other anti-carcinogenic compounds [97]. Several large prospective studies examining this relationship have reported nearly null results [98].

1.4.2.9. Alcohol

Alcohol repeatedly has been shown to increase breast cancer risk. In 2007, the International Agency for Research on Cancer stated there was sufficient evidence to conclude that alcohol causes cancer of the female breast [99]. Alcohol likely infers risk through its effect plasma concentrations of estrogen. An analysis of subjects enrolled in the Women's Health Study found a significant 43% increased risk for invasive breast

cancer among those who consumed at least 30 grams of alcohol daily compared to those who did not report consumption [100]. Consumption has also been shown to increase the risk of recurrence. One study reported risk of recurrence as 1.3 times greater among those consumed three to four or more drinks per week. In addition, this association was stronger among post-menopausal and overweight or obese women [101].

1.4.2.10. Obesity

Obesity and weight gain during adult years are associated with increased risk of breast cancer, especially among post-menopausal women. In 2002, the International Agency for Research on Cancer concluded that there was adequate evidence to support an association between obesity and post-menopausal breast cancer [102]. There are several biological mechanisms through which factors related to being overweight or obese may exert their effect on breast carcinogenesis. Obese women have been found to have 35% higher concentrations of estrogen and 130% higher concentrations of estradiol compared to women classified as non-obese. In addition, increasing levels of adiposity are also associated with increasing plasma concentrations of testosterone. A strong inverse association is also present between obesity and sex-hormone-binding globulin (SHBG) levels. Low plasma quantities of SHBG contribute to the bioavailability of androgens and estrogen. Obese women also likely have concomitant hyperinsulinaemia which may stimulate mammary carcinogenesis through increasing levels of insulin-like growth factor and leptin [103]. Among post-menopausal women, the risk of breast cancer has been reported to be 50% higher among those who gained between 15 and 20 kilograms compared to women who maintained their weight [104]. High BMI is also associated with

a small increase in risk for larger tumors due to enhanced proliferation attributable to higher concentrations of circulating hormones which promote growth [105].

1.4.2.11. Family history

About 7% of breast cancer cases are attributable to inherited genetic mutations. Two such susceptibility genes that carry mutations are breast cancer susceptibility gene 1(BRCA1) and breast cancer susceptibility gene 2 (BRCA2). These genes are tumor suppressors located on the long arms of chromosomes 17 and 13. BRCA1 and BRCA2 proteins aid in double-strand break repair following damage to DNA. They also function as transcriptional co-regulators [106]. The highest population prevalence rates of these genes have been found among Ashkenazi Jews. The cumulative lifetime risk for women who carry mutations in either BRCA1 or BRCA2 can be as high as 80%. On average, neoplasms of the breast found among carriers of these mutations are of a higher grade than those of non-carriers [107]. In addition, women with these familial genes likely will have an earlier age at onset compared to sporadic cases [108]. A carrier of a BRCA1 or BRCA2 mutation has almost a 3% risk of being diagnosed with breast cancer before age 30. This risk increases to about 50% by age 50 and increases again to between 50% and 80% by age 70 [109].

1.4.3. Rationale for analyses

Studies of disease incidence in migrant populations residing in their host countries offer vital insight into factors, both environmental and genetic, that play a role in etiology. Migrant populations have been found to experience a change in risk for breast cancer that

differs from the risk of their native countries. Thus, this change is likely due to environmental factors that contribute to disease [110]. Migrant studies examining breast cancer mortality have also suggested the importance of behavioral factors as significant indicators of disease outcomes [111].

In the U.S. today, breast cancer incidence rates have been found to differ significantly by racial/ethnic groups. When examining individual groups, the lowest overall rates are found among Asians. In addition, there are substantial differences in incidence within the Asian group alone. It has been reported that there is likely almost a three-fold difference in incidence rates of breast cancer between the populations with the highest (Japanese) and lowest (Laotian) rates. Closer examination of specific Asian populations may reveal significant heterogeneity in lifestyles, risk factors, and health care behaviors that all contribute to differences in cancer outcomes [112]. When examining Asians living in the U.S, it has been found that these populations are heterogeneous with regard to immigration and acculturation. These two factors likely play a significant role in explaining varying cancer outcomes [113]. Previous studies conducted in the U.S. examining breast cancer incidence among Asian subpopulations in the U.S. are summarized in **Table 1-4**. We aim to update these findings and examine differences in stage at diagnosis and survival among Asian subpopulations in the U.S.

1.5. List of References

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1.6. Tables and Figures

Table 1-1: Characteristics of studies examining liver cancer incidence among Asian subpopulations in the U.S.

Reference	Source of data	Asian subpopulations examined	Comparison of incidence (Asian vs. NHW[1])
McCracken et al, 2007 [1]	California Cancer Registry	Chinese, Filipino, Vietnamese, Korean, Japanese	Asian > NHW
Jain, Mills, Parikh-Patel, 2005 [38]	California Cancer Registry	South Asians	Asian > NHW
Rosenblatt, Weiss, Schwartz, 1996 [39]	SEER (Hawaii & San Francisco/Oakland only)	Chinese, Japanese, Filipino	Asian > NHW
Miller et al, 2008 [4]	SEER 14	South Asians, Chinese, Filipino, Japanese, Korean, Vietnamese, Laotians	Asian > NHW
Chang et al, 2010 [40]	California Cancer Registry	Chinese, Japanese, Filipino, Korean	N/A (Asian > Hispanics)
Chang et al, 2007 [15]	Greater Bay Area Cancer Registry	Chinese, Japanese, Filipino, Korean, Vietnamese	Asian > NHW
Kwong et al, 2005 [2]	California Cancer Registry	Chinese, Japanese, Filipino, Korean, Vietnamese	N/A
Gomez et al, 2003 [41]	SEER and California Cancer Registry	Korean	Asian > NHW
Le et al, 2002 [42]	SEER and California Cancer Registry	Vietnamese	Asian > NHW

[1]NHW= non-Hispanic white

Figure 1-1: Age-adjusted incidence rates of liver cancer in the U.S. comparing Asian/PI and non-Hispanic whites, 1999-2009

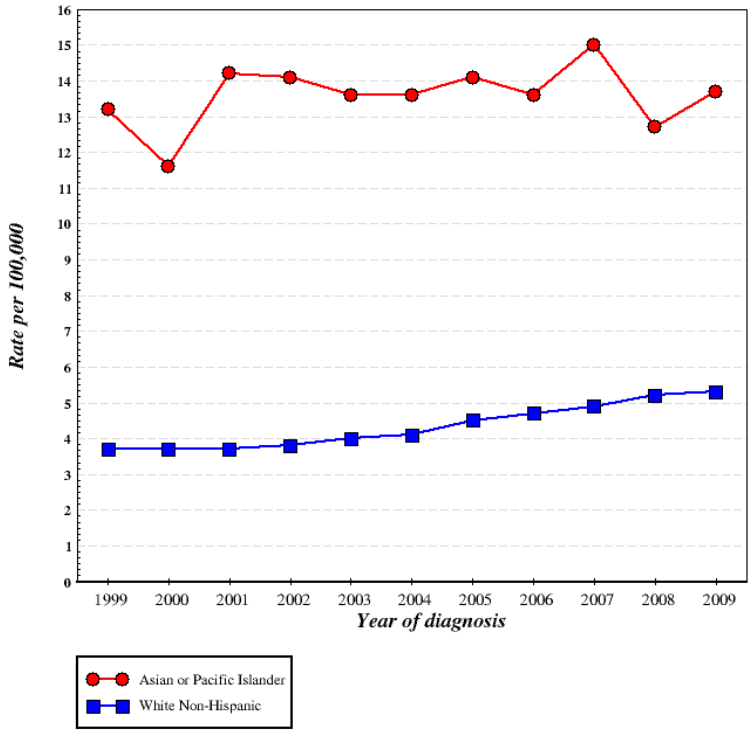


Figure 1-2: Liver cancer stage at diagnosis in the U.S. by race/ethnicity

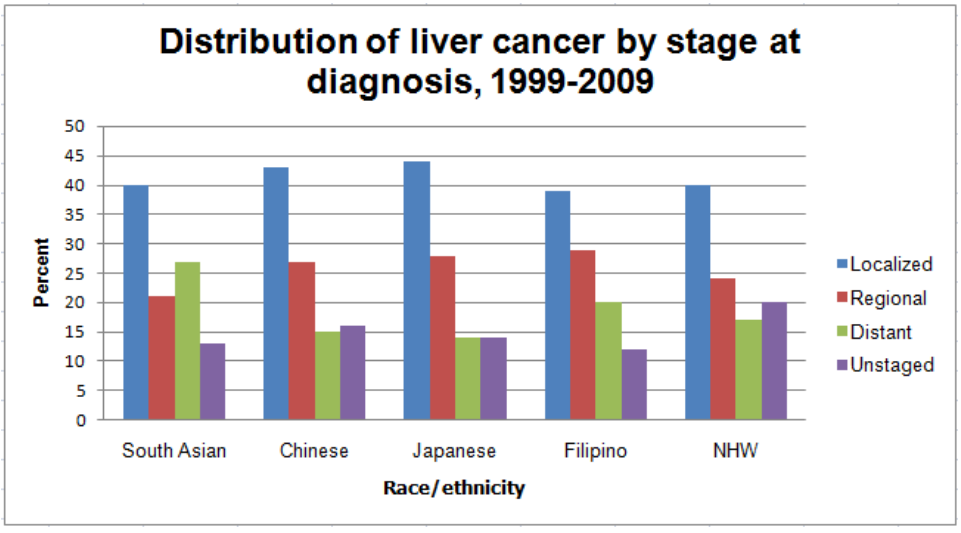


Table 1-2: Characteristics of studies examining stomach cancer incidence among Asian subpopulations in the U.S

Reference	Source of data	Subpopulations examined	Comparison of incidence (Asian vs. NHW[1])
McCracken et al, 2007 [1]	California Cancer Registry	Chinese, Filipino, Vietnamese, Korean, Japanese	Asian> NHW
Kamineni et al, 1999 [57]	SEER (Hawaii, San Francisco/Oakland, Washington only)	Chinese, Japanese, Filipino	Asian> NHW
Kwong et al, 2005 [2]	California Cancer Registry	Chinese, Filipino, Japanese, Korean, Vietnamese	N/A
Gomez et al, 2003 [41]	SEER, California Cancer Registry, IARC	Korean	Korean> NHW
Miller et al, 2008 [4]	SEER	Chinese, Filipino, Japanese, Korean, Vietnamese, South Asian	Asian> NHW
Le et al, 2002 [42]	SEER, California Cancer Registry, IARC	Vietnamese	Vietnamese> NHW
Yang, Mills, Riordan, 2005 [58]	California Cancer Registry	Hmong	Hmong> NHW

[1]NHW= non-Hispanic white

Figure 1-3: Age-adjusted incidence rates of stomach cancer in the U.S. comparing Asian/PI and non-Hispanic whites, 1999-2009

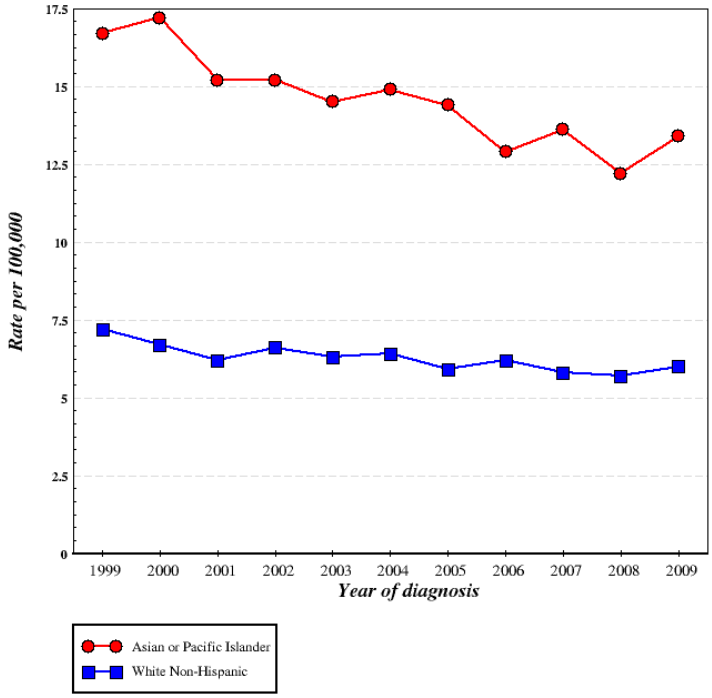


Figure 1-4: Stomach cancer stage at diagnosis in the U.S. by race/ethnicity

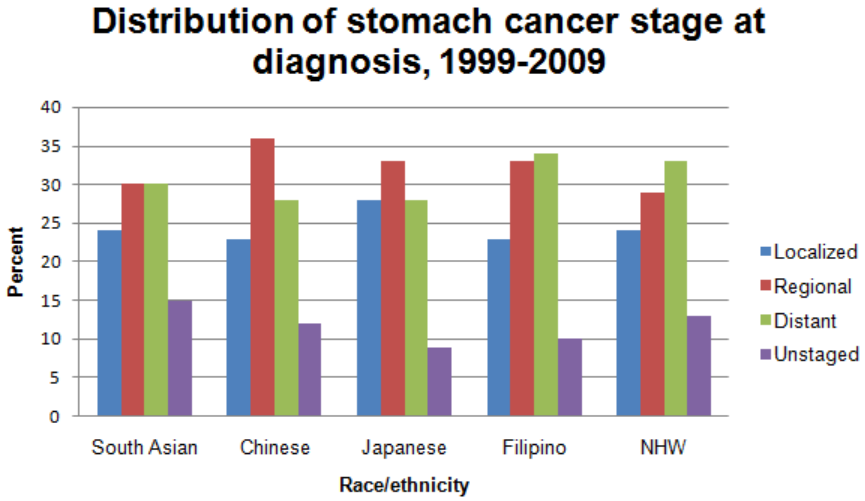


Table 1-3: Characteristics of studies examining cervical cancer incidence among Asian subpopulations in the U.S.

Reference	Source of data	Subpopulations examined	Comparison of incidence (Asian vs. NHW[1])
Bates et al, 2008 [77]	California Cancer Registry	Chinese, Japanese, Filipino, Korean, South Asian, Vietnamese	Vietnamese, Korean> NHW
McCracken et al, 2007 [1]	California Cancer Registry	Chinese, Filipino, Vietnamese, Korean, Japanese	Asians> NHW
Wang et al, 2010 [80]	SEER (Hawaii, LA, Seattle, San Francisco-Oakland, San Jose-Monterey only)	Chinese, Filipino, Japanese, Vietnamese, Korean, South Asian	Asians> NHW
Jain, Mills, Parikh-Patel, 2005 [38]	California Cancer Registry	South Asian	South Asians> NHW
Gomez et al, 2003 [41]	SEER and California Cancer Registry	Korean	Korean> NHW
Le et al, 2002 [42]	SEER and California Cancer Registry	Vietnamese	Vietnamese> NHW
Miller et al, 2008 [4]	SEER	Chinese, Filipino, Japanese, Korean, Vietnamese, South Asian	Asians> NHW

[1]NHW= non-Hispanic white

Figure 1-5: Age-adjusted incidence rates of cervical cancer in the U.S. comparing Asian/PI and non-Hispanic whites, 1999-2009

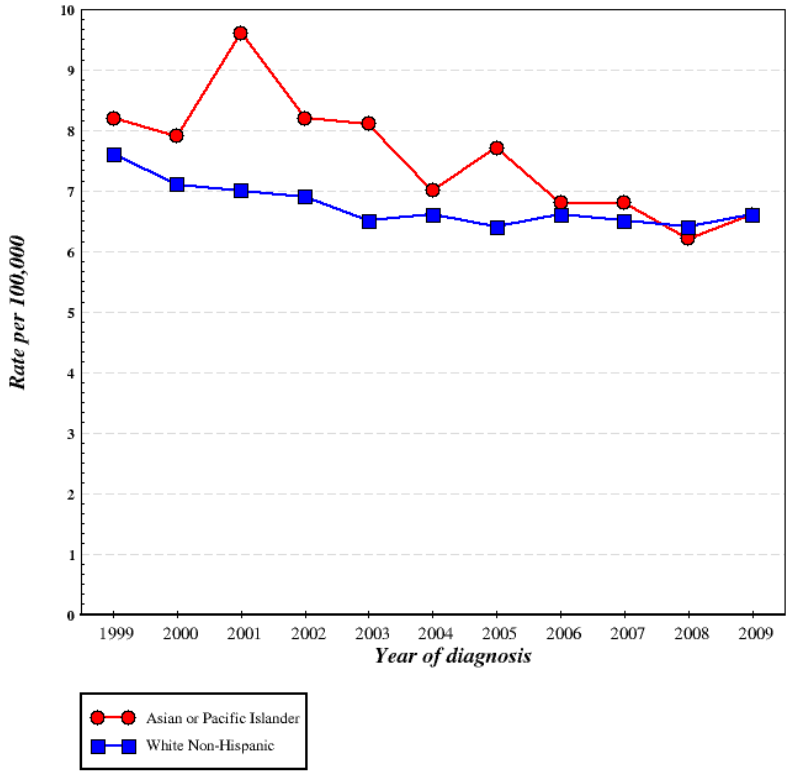


Figure 1-6: Cervical cancer stage at diagnosis in the U.S. by race/ethnicity

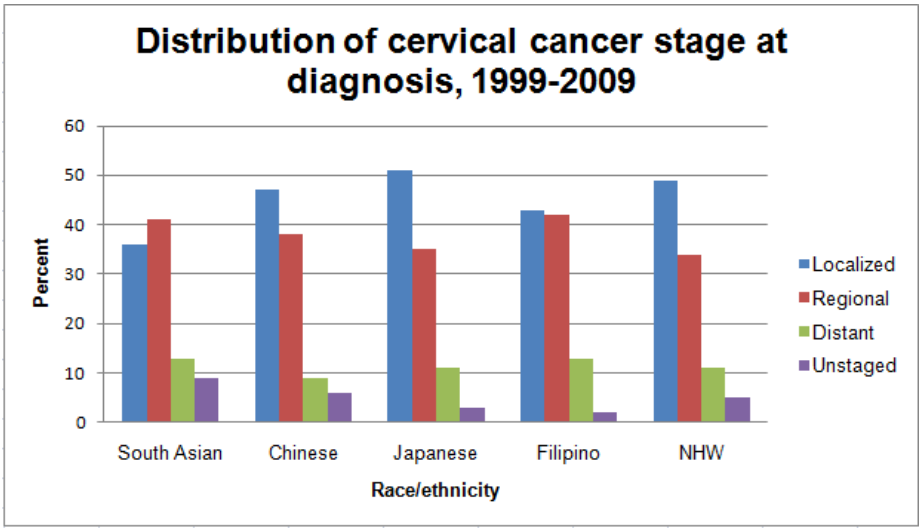


Table 1-4: Characteristics of studies examining breast cancer incidence among Asian subpopulations in the U.S.

Reference	Source of data	Asian subpopulations examined	Comparison of incidence (Asian vs NHW[1])
Moran et al, 2011 [114]	SEER	South Asian	South Asian< NHW
Goggins & Wong, 2009 [5]	SEER	South Asian	South Asian< NHW
Keegan et al, 2007 [115]	Greater Bay Area (SEER)	Chinese, Japanese, Filipino, Korean, South Asian, Vietnamese	N/A
Stanford et al, 1995 [111]	SEER (Hawaii, San Francisco/Oakland, Washington)	Chinese, Japanese, Filipino	Asian< NHW
Deapen et al, 2002 [116]	Los Angeles Cancer Surveillance Program	Chinese, Japanese, Filipino, Korean	Asian< NHW
Miller et al, 2008 [4]	SEER	Chinese, Japanese, Filipino, Korean, South Asian, Vietnamese	Asian< NHW
McCracken et al, 2007 [1]	California Cancer Registry	Chinese, Filipino, Vietnamese, Korean, Japanese	Asian< NHW
Gomez et al, 2010 [112]	California Cancer Registry	Chinese, Japanese, Filipino, Korean, South Asian, Vietnamese	Asian< NHW
Kwong et al, 2005 [2]	California Cancer Registry	Chinese, Filipino, Japanese, Korean, Vietnamese	N/A

[1]NHW= non-hispanic white

Figure 1-7: Age-adjusted incidence rates of breast cancer in the U.S. comparing Asian/PI and non-Hispanic whites, 1999-2009

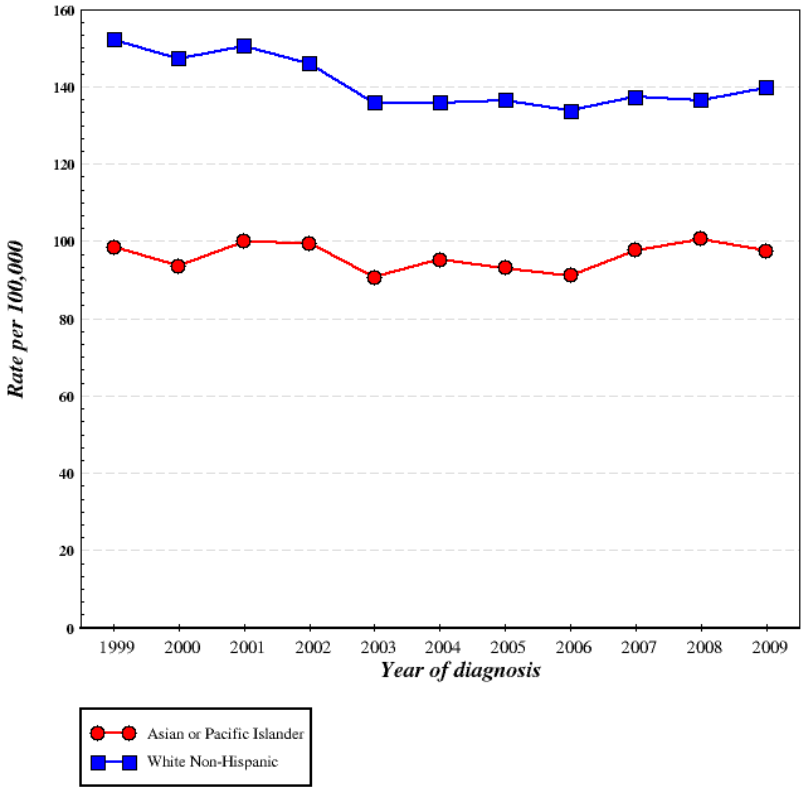
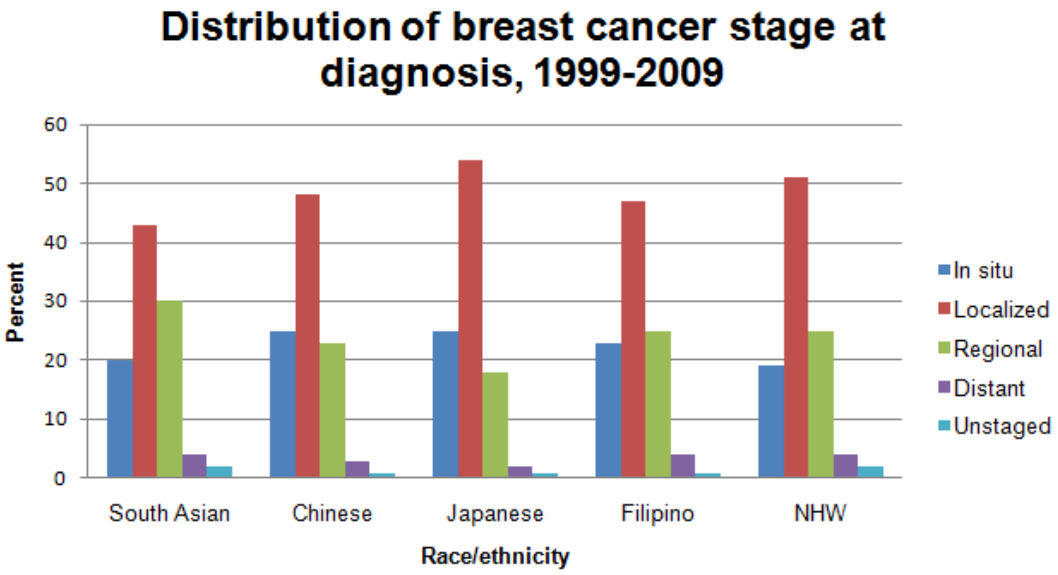


Figure 1-8: Breast cancer stage at diagnosis in the U.S. by race/ethnicity



2. STAGE AT DIAGNOSIS AND STAGE-SPECIFIC SURVIVAL OF INFECTION-ASSOCIATED (CERVICAL, LIVER, STOMACH) CANCERS AMONG SOUTH ASIANS AND OTHER ASIAN SUBPOPULATIONS IN THE UNITED STATES

2.1. Abstract

Though Asian Americans report low rates for major cancers, such as lung, colon, and prostate, they report high rates of cancers associated with infectious agents, including cancers of the cervix, liver, and stomach. South Asians comprise a major Asian American subpopulation whose cancer burden has not been adequately examined and documented in the literature. In order to better understand and address the outcomes associated with infection-associated cancers in the South Asian population in the U.S., we examined this group separately from the other predominant Asian subpopulations in the country. Through use of data from the Surveillance, Epidemiology, and End Results (SEER) program, we assessed differences in stage at diagnosis and stage-specific survival of these cancers among South Asians and other Asian subpopulations (Chinese, Japanese, Filipino) compared to non-Hispanic whites in the U.S. Logistic regression was utilized to examine the association between South Asian race and stage at diagnosis. Stage-specific survival following cancer diagnosis was also examined among the racial groups of interest using proportional hazards models. Place of birth was found to be associated with a decreased risk of late stage diagnosis of cervical cancer among those that were foreign-born compared to those that were U.S.-born (OR=0.92; 95% CI 0.84, 1.00). Foreign-born cases had an increased risk of late stage diagnosis of stomach cancer compared to those that were U.S.-born (OR=1.08; 95% CI 1.00, 1.16). Among cervical

cancer cases diagnosed at late stage, Asians had a significant decreased risk (HR=0.76; 95% CI 0.65, 0.87) of death compared to non-Hispanic whites. Decreased risk (HR=0.89; 95% CI 0.84, 0.95) of death was found for foreign-born cases diagnosed at early stage of liver cancer compared to U.S.-born cases. Foreign-born stomach cancer cases had significant decreased risk of death compared to those that were U.S.-born at both early (HR=0.77; 95% CI 0.71, 0.83) and late (HR=0.88; 95% CI 0.85, 0.92) stages. Our study findings indicated that the Asian subpopulations examined in our analyses had more favorable outcomes related to stage at diagnosis and stage-specific survival when compared to non-Hispanic whites. However, future research should specifically examine these outcomes in South Asian patients in the U.S.

2.2. Background

Cancer is a significant cause for public health concern among Asian Americans residing in the U.S. This racial/ethnic population is the only one for which the number of deaths annually attributable to cancer exceeds that of heart disease. Though this group reports low rates for major cancers, such as lung, colon, and prostate, they report high rates of cancers associated with infectious agents. These include cancers of the cervix, liver, and stomach [1]. Though they are the third largest Asian subpopulation in the U.S. [2], South Asians comprise a group whose cancer outcomes have not been well examined and documented in the literature [3].

A previous study which examined the burden of cervical cancer among Asian subpopulations using data from the California Cancer Registry revealed heterogeneity in incidence and mortality. It was found that incidence rates among Asian women in the U.S. broadly mirrored those in their countries of origin. However, the exception to this general finding was found among South Asian women. Though relatively high cervical cancer incidence rates are found in India, South Asian women living in California had the lowest rates compared to the other subpopulations. This difference in rates is likely attributable to the high level of education found among South Asians in the U.S. compared to other Asian subpopulations. This study also reported more favorable survival among South Asians compared to non-Hispanic whites [4]. Our study aims to extend on these findings by also examining stage at diagnosis and place of birth as a risk factor associated with outcomes among South Asians and other Asian subpopulations through use of data from all available SEER registries in the U.S.

Approximately 60-80% of liver cancer cases in the Asian/Pacific Islander population are due to infection with hepatitis B virus (HBV). Those that comprise this racial/ethnic group originate from countries where HBV infection is endemic. In addition, most of these chronic infections were likely acquired before adulthood. The significant racial/ethnic disparity in burden of chronic HBV infection in the U.S. is largely due to the fact that 67% of the Asian/Pacific Islander population is foreign-born. Due to the high prevalence of chronic infection in this population, liver cancer incidence is more than 3-fold higher among males of Asian/Pacific Islander origin compared to white males [5]. Though the South Asian population is rapidly growing in the U.S., the liver cancer burden of this group has not been extensively examined. A previous study reported a slight survival advantage for South Asians compared to whites [3]. We aim to build on these results by also examining risk of late stage diagnosis and the association of place of birth with stage-specific survival.

Helicobacter pylori (*H. pylori*), a gram-negative spiral bacterium known to infect nearly half of the global population, is the most well-known risk factor for stomach cancer [6]. There is widespread geographic variation in seroprevalence rates of *H. pylori* infection in Asia. India is classified as a low-risk region for stomach cancer where the age-standardized incidence rate is about 5.7 per 100,000 despite relatively high seroprevalence of infection reported at 79%. In contrast, high-risk regions for stomach cancer (Japan, China, Korea) where the seroprevalence ranges from 39.3% to 59.6% report age-standardized incidence rates ranging from 41.4 to 69.7 per 100,000. This paradox is referred to as the “Asian Enigma” and is likely attributable to host genetic

factors and other environmental exposures such as diet and smoking which also affect stomach cancer risk [7]. The presence of this phenomenon does not allow for accurate estimates of stomach cancer burden if various Asian subpopulations are combined to create one aggregate group known as Asian/Pacific Islander. It has also been found that despite higher incidence of stomach cancer, Asian countries have consistently reported more favorable outcomes related to disease compared to Western countries. This can be seen when examining 5-year survival in Japan (40-60%) compared to the U.S. and Europe (15-20%) [8]. This finding is consistent with a previous study which examined stomach cancer incidence and survival among South Asians where this group had more favorable survival compared to whites [3]. Our study aims to extend on these results by also examining risk of late stage diagnosis and the association of place of birth with stage-specific survival.

In order to better understand and address the outcomes associated with infection-associated cancers in the South Asian population in the U.S., this study will examine this group separately from the other predominant Asian subpopulations in the country. Through use of data from the Surveillance, Epidemiology, and End Results (SEER) program of the National Cancer Institute (NCI), we aim to examine differences in stage at diagnosis and stage-specific survival of these cancers among South Asians and other Asian subpopulations (Chinese, Japanese, Filipino) compared to non-Hispanic whites in the U.S.

2.3. Methods

Our study population included all cases identified as South Asian, Chinese, Japanese, Filipino, or non-Hispanic white diagnosed with incident primary invasive cervical, liver, or stomach cancers between January 1, 1999 and December 31, 2009 among 17 population-based cancer registries included in the SEER program. South Asian race is defined in our study as those originating from either India or Pakistan as classified by SEER. These two countries of origin have been combined to create one racial/ethnic category in SEER since 1988. The following registries were included in our analyses: San Francisco-Oakland, Los Angeles, San Jose-Monterey, Greater California, Connecticut, Detroit, Hawaii, Iowa, New Mexico, Seattle- Puget Sound, Utah, Atlanta, Greater Georgia, Rural Georgia, Kentucky, Louisiana, and New Jersey. Patient data were ascertained by SEER from medical records and available information for each diagnosed case included demographics, tumor characteristics at diagnosis, and year of diagnosis.

Patients were selected for inclusion in the cervical cancer analysis if they were assigned SEER tumor site codes C530-C539. Cases diagnosed with hepatocellular carcinoma were selected for the liver cancer analysis using tumor site code C220. In addition, to ensure that cholangiocarcinomas were excluded only cases with ICD-O-3 histology codes 8170-8175 were selected for inclusion. Stomach cancer cases were identified using tumor site codes C160-169. Only gastric adenocarcinoma patients classified using the following ICD-O-3 histology codes were selected for inclusion: 8000-8001, 8010, 8020-8021, 8050, 8140-8221, 8255-8560, and 8570-8576. Those less than 18 years at

diagnosis or with unknown age at diagnosis were excluded. Those with in situ or unknown stage at diagnosis were also excluded.

We also examined place of birth as a variable of interest in our study. Subjects were classified as either "U.S.-born" or "foreign-born" based on data extracted by SEER from patient medical records or death certificates. Since one principal aim of this study was to make inferences regarding the effect of U.S. versus foreign birth on subsequent cancer outcomes, those with unknown place of birth were excluded from our analyses. The final sample sizes used for analysis for each cancer were as follows: 13,982 for cervical, 16,672 for liver, and 23,553 for stomach. **Figure 2-1** is a graphical depiction of the exclusions which produced the final analytic sample for each cancer. In addition, demographic and tumor characteristics of the eligible Asian cases prior to these exclusions are shown in **Appendix A**.

Several covariates were considered to be potential confounders in our analyses. The models used in the logistic regression analysis adjusted for the effects of age at diagnosis, sex, year of diagnosis, and SEER registry. Age is adjusted for as a confounder due to its varying distributions in the racial/ethnic subpopulations examined and due to the association between older age and increased risk of cancer. Sex is considered as a potential confounder to take into account genetic and lifestyle differences which may differ by racial/ethnic group and affect the outcome of disease. Year of diagnosis is taken into account since diagnosis and surveillance methods for cancer detection may have varied during the time period of our study. SEER registry is adjusted for to take into

account the location from which the cases originated since access to care and likelihood of diagnosis may vary between locations. The models used in the survival analysis also adjusted for the effect of grade in addition to the covariates used in the logistic regression analysis. Grade is a tumor characteristic taken into account due to its effect on survival, since increasing grade is associated with poorer prognosis. In addition, grade at diagnosis may vary due to genetic differences between the racial/ethnic subpopulations being compared.

The primary relationship of interest in the logistic regression analysis was the association of South Asian race on cancer stage at diagnosis. Subjects were categorized as having early or late stage disease, with the outcome of interest defined as late stage at diagnosis. Cervical cancer patients with AJCC stage IA-IIA at diagnosis were classified as early stage and those with stage greater than IIA were classified as late stage. Liver cancer cases were categorized using a combination of SEER summary stage (for cases diagnosed 1999-2003) and AJCC stage (for cases diagnosed 2004-2009). Cases with SEER summary stage as 'localized' or 'regional by direct extension' were categorized as early stage and those with higher stages were categorized as late stage. Cases with AJCC stage I-II were classified as early stage and those with stage III or greater were classified as late stage. The same method combining SEER summary stage and AJCC stage was used for early and late stage classification of stomach cancer.

Logistic regression was conducted to obtain odds ratios and their 95% confidence intervals to examine the association between race and late stage at diagnosis. Age-

adjusted associations were first obtained using models with only race and age as predictors. Adjusted associations were then examined which controlled for other potential confounders. We also examined the effect of place of birth by including it as a predictor along with race and the other covariates. Non-Hispanic whites served as the referent racial group in all models.

Stage-specific survival following cancer diagnosis was also examined among the subpopulations of interest. Survival time was provided as a variable in the SEER database and was calculated by using the date of diagnosis and the earliest of the following: date of death, date last known to be alive, or the follow-up cutoff date of December 31, 2009. In addition, vital status was provided in the data as either "alive" or "dead." The Kaplan-Meier method was utilized to test differences in overall survival between the racial groups being compared through use of the log-rank test. Cox proportional hazards regression was utilized for multivariate adjustment to control for the effects of age, sex, SEER registry, stage, and grade on the observed differences in survival. The proportional hazards (PH) assumption was assessed for these covariates prior to inclusion in the models through use of log-log plots and goodness-of-fit tests. Hazard ratios and 95% confidence intervals were obtained to examine the association between race and stage-specific survival. Age-adjusted associations were obtained using models with only race and age as predictors. Adjusted estimates were then examined which controlled for potential confounders. We also examined the effect of place of birth by including it as a predictor along with race and the other covariates. All analyses were conducted using SAS, version 9.3 (SAS Institute, Inc., Cary, NC).

2.4. Results

Tables 2-1 through **2-3** show the distributions of demographic and tumor characteristics for each cancer examined by race. Due to small sample sizes within the individual Asian subpopulations for cervical cancer, all Asians (Chinese, Japanese, Filipino, South Asians) were combined to create an aggregate racial/ethnic category and compared with non-Hispanic whites for both the stage at diagnosis and stage-specific survival analyses. As seen in **Table 2-1**, the mean age at diagnosis was slightly higher for Asian cases compared to non-Hispanic whites. **Table 2-2** shows the distribution of demographic and tumor characteristics for liver cancer. The proportion of male and female cases was almost the same among Japanese while the majority of cases for the other subpopulations were male. In addition, South Asians had the highest proportion of late stage cases compared to the other Asian subpopulations and non-Hispanic whites. The distribution of these characteristics for stomach cancer is shown in **Table 2-3**. South Asians had the youngest mean age at diagnosis and the highest proportion of late stage cases. The highest proportion of cardia tumors was seen among non-Hispanic whites (35.3%), while non-cardia tumors accounted for more than half of the tumors found among the Asian subpopulations examined.

Stage at diagnosis

Cervical

As seen in **Table 2-4**, it was found that Asians had a non-significant slightly increased risk (9%) of late stage diagnosis when compared to non-Hispanic whites in the fully adjusted model which controlled for the effects of age, year of diagnosis, SEER registry,

and place of birth. When examining the independent effect of place of birth among all subjects, it was found that foreign-born cases had significantly decreased risk of late stage diagnosis compared to U.S. born cases. The combined effect of Asian race and place of birth was also examined in separate models. However, the effect estimates obtained in these models were found to be close to null and non-significant.

Liver

Table 2-5 shows the results of the stage at diagnosis analysis for liver cancer. As can be seen in the effect estimates, there was notable heterogeneity among the Asian subpopulations examined. South Asians and Filipinos were the most similar when comparing their risks of late stage diagnosis to non-Hispanic whites. Though non-significant, there was 28% increased risk of late stage diagnosis among South Asians when compared to non-Hispanic whites. The effect of place of birth was close to null and non-significant for this cancer site.

Stomach

Table 2-6 shows the results of the stage at diagnosis analysis for stomach cancer. Effect estimates obtained for the fully adjusted model did not differ greatly among the Asian subpopulations. When compared with non-Hispanic whites, the odds ratio obtained for South Asians was close to null. Place of birth had a modest effect when examining all subjects, with foreign-born cases having an increased 8% risk of late stage diagnosis compared to U.S.-born cases. However, place of birth did not have a significant effect when examining Asians alone.

Stage-specific survival

Cervical

Unadjusted Kaplan-Meier curves examining overall cervical cancer survival comparing our Asian subpopulations of interest and non-Hispanic whites are shown in **Appendix B**. The log-rank test p-value which can be used to detect significant differences in the survival curves is also shown. Asians in our subpopulations of interest had more favorable unadjusted overall survival compared to non-Hispanic whites. The log-rank test p-value of <.0001 indicated significant difference in the survival curves between the racial/ethnic groups being compared.

Table 2-7 shows results from the cervical cancer survival analysis. Asians had lower risk of death among those diagnosed at both early and late stages when compared to non-Hispanic whites in all of the models used. This decreased risk of death became almost null in the fully adjusted models which also accounted for place of birth. When examining place of birth as an independent predictor, it was found that foreign-born cases had significant decreased risk of death compared to U.S.-born cases for both early and late stages. We also examined the effect of place of birth among Asians only with U.S.-born Asians as the referent group (results not shown). According to these models, a significant decreased risk (HR=0.57; 95% CI 0.39, 0.83) was found for foreign-born Asians diagnosed at late stage compared to U.S.-born Asians.

Liver

Unadjusted Kaplan-Meier curves examining overall liver cancer survival comparing South Asians to the other Asian subpopulations and non-Hispanic whites are shown in

Appendix B. South Asians had the worst overall unadjusted survival compared to the other Asian subpopulations. The log-rank test p-value of <.0001 indicates significant difference in the survival curves between the racial/ethnic groups being compared.

Table 2-8 shows the results from the liver cancer survival analysis. There was notable heterogeneity in the hazard ratios obtained for those diagnosed at early stages, with the lowest risk of death found among Chinese and the highest risk among Filipino. The risk of death obtained for South Asians compared to non-Hispanic whites was almost null for both early and late stages. A significant decreased risk of death was obtained for foreign-born cases compared to those that were U.S.-born among those diagnosed at early stages.

Stomach

Unadjusted Kaplan-Meier curves examining overall stomach cancer survival comparing South Asians to the other Asian subpopulations and non-Hispanic whites are shown in **Appendix B**. South Asians had the worst overall unadjusted overall compared to the other Asian subpopulations. The log-rank test p-value of <.0001 indicates significant difference in the survival curves between the racial/ethnic groups being compared.

Table 2-9 shows the results from the stomach cancer survival analysis. Though there was notable heterogeneity in the hazard ratios obtained among those with early stage diagnosis, they did not differ greatly among those with late stage diagnosis. Significant decreased risk of death was found among foreign-born cases compared to those that were U.S.-born for both early and late stage cases in both models.

It has been previously reported that despite higher incidence of stomach cancer, Asian countries consistently report more favorable outcomes related to the disease compared to Western countries. A potential reason for these variations in survival between regions likely involves inherent differences in tumor biology. In Western countries, proximal (cardia) gastric tumors are more common while the majority of tumors found in Asia are distal (non-cardia) tumors [8]. This trend was observed among our sample of stomach cancer cases found in SEER since the majority of non-cardia tumors were found among the Asian patients. Risk factors such as obesity and white race/ethnicity are linked with cardia tumors [9]. In addition, it has been reported that tumors found in the gastric cardia are associated with more unfavorable prognosis compared to those found at other sites in the stomach [10]. This likely contributes to the decreased risk of death found among the Asian subpopulations compared to non-Hispanic whites and those that were foreign-born compared to U.S.-born.

We assessed differences in the outcomes of interest in our study while accounting for these gastric tumor subsites (cardia versus non-cardia). When examining stage at diagnosis, those with cardia tumors had 8% decreased risk (OR=0.92; 95% CI 0.86, 0.99) of late stage diagnosis compared to those with non-cardia tumors after adjustment for confounders. Among those diagnosed at early stage, cases with cardia tumors had 20% increased risk (HR=1.20; 95% CI 1.12, 1.29) of death compared to those with non-cardia tumors in the fully adjusted model. The effect of place of birth on stage-specific survival was examined after restricting cases by subsite. The results of these analyses are shown in **Table 2-10**. As seen in the table, the effect of foreign birth did not vary greatly

between early and late stage cases among those with cardia tumors. There was a greater protective effect of foreign birth at early stage diagnosis among those with non-cardia tumors.

2.5. Discussion

This study found notable heterogeneity when examining stage-specific survival of three common infection-associated cancers among Asian subpopulations. Controlling for the effects of potential confounders such as age at diagnosis, sex, SEER registry, and grade did not diminish the heterogeneity of these effects. In addition, it was also found that those that were foreign-born had significantly more favorable survival associated with these cancers compared to those that were U.S.-born.

Due to limited sample sizes, all Asians were combined to create one aggregate racial/ethnic group in the analysis which examined differences in risk of late stage diagnosis of cervical cancer. The fully adjusted model which controlled for the effects of confounders and place of birth produced an odds ratio which was almost null and thus non-significant. However, the independent effect of place of birth was found to be associated with a decreased risk of late stage diagnosis among those that were foreign-born compared to those that were U.S.-born (OR=0.92; 95% CI 0.84, 1.00). Human papillomavirus (HPV) has long been identified as a necessary cause of cervical cancer. The natural history of cervical cancer begins by acquiring a sexually transmitted carcinogenic HPV infection [11]. Virtually all cases are attributable to persistent infection with one of almost 15 types of oncogenic HPV genotypes [12]. Several studies have found an association between smoking and increased risk of cervical cancer and its immediate

precursor, cervical intraepithelial neoplasia grade 3 (CIN3). A study examining the role of smoking as a risk factor for CIN3 among HPV-positive women found that current smokers (OR=1.70; 95% CI 1.40, 2.10) and past smokers (OR=1.70; 95% CI 1.20, 2.40) were at increased risk for CIN3 or cancer compared to non-smokers. In addition, greater intensity of smoking and duration strengthened the magnitude of this association. It is likely that smoking exerts an effect on the interaction between HPV infection and biological processes in the host through a mechanism which increases the likelihood of pre-malignant change in the cervix. Since carcinogenic metabolites produced through smoking have been detected in cervical secretions, smoking may increase the risk for CIN3 by promoting viral persistence or through producing genomic damage through genotoxins [13]. This association between smoking and increased risk for CIN3 may provide an explanation for the decreased risk of advanced stage diagnosis found among foreign-born women. It has been reported that the prevalence of smoking among women in the U.S. is about 13.3-16.5%. This is in comparison to prevalence of less than 9.8% among women in Asia [14].

With the exception of Filipino cases, our study did not find significant odds ratio estimates for the risk of late stage diagnosis of liver cancer. However, it is of clinical significance to note that South Asians had the highest proportion (48%) of late stage cases compared to the other Asian subpopulations examined. The non-significance of the effect estimate produced for South Asians in our analysis was likely due to the small sample size of this subpopulation. The importance of diabetes as an independent risk factor for liver cancer has emerged in recent studies of this disease. A study conducted in

the U.S. reported that diabetes was associated with a 2-3 fold increased risk of hepatocellular carcinoma, regardless of the presence of other major risk factors such as HBV, HCV, and alcoholic liver disease [15]. This is association between diabetes and liver cancer is of particular importance to the South Asian population. India reports the highest prevalence of diabetes compared to other countries in this region, with rates ranging from 18.6% in urban areas to 9.2% in rural areas [16]. A study conducted in India found that diabetic patients diagnosed with hepatocellular carcinoma had more advanced tumors of larger size and increased likelihood of intraheptic bile duct involvement [17]. These findings highlight the need for improved monitoring among those of South Asian origin who are diabetic or diagnosed with other risk factors for hepatocellular carcinoma in order to increase the likelihood of early stage diagnosis.

Our study did not find notable differences in risk of late stage diagnosis of stomach cancer among the Asian subpopulations compared to non-Hispanic whites. However, those that were foreign-born had an increased risk of late stage diagnosis compared to those that were U.S.-born (OR=1.08; 95% CI 1.00, 1.16). This increased risk is likely attributable to differences in dietary intake between those who are foreign born compared to U.S.-born. Salt intake has been shown to be a risk factor for gastritis and amplify the effects of gastric carcinogens. Mucosal damage caused by salt intake also likely increases the risk for persistent infection with *H. pylori* [18]. It has also been hypothesized that *H. pylori* infection acts synergistically with dietary factors to promote carcinogenesis [19]. *H. pylori* prevalence rates vary greatly between Asia and North America, ranging from 80% in India to 30% in the U.S. and Canada [20]. In addition, dietary salt intake is

considered high in the Asian subpopulations examined in our study. Intake of spicy and pickled foods and dried salted meats are significant dietary behaviors which are likely associated with advanced stage diagnosis in India and other Asian countries [21].

Our study found that Asians had more favorable stage-specific survival for cervical cancer compared to non-Hispanic whites. In addition, those that were foreign born had decreased risk of death compared to those that were U.S.-born. In the adjusted model which controlled for age at diagnosis, SEER registry, and grade it was found that among those diagnosed at late stage, Asians had a significant decreased risk (HR=0.76; 95% CI 0.65, 0.87) of death compared to non-Hispanic whites. This risk became close to null (HR=0.94; 95% CI 0.81, 1.10) when place of birth was added to the model. In addition, the independent effect of place of birth was statistically significant among both early (HR=0.76; 95% CI 0.66, 0.88) and late (HR=0.66; 95% CI 0.61, 0.72) stage cases. Survival outcomes associated with cervical cancer among Asian subpopulations have not been studied extensively in the U.S. Our findings are consistent with a study among Asian subpopulations conducted in California which reported more favorable survival outcomes for these groups compared to non-Hispanic whites. This study also concluded that differences in histology did not affect the risk estimates obtained [4]. Another study examining survival differences for cervical cancer in Asian subpopulations reported more favorable unadjusted cause-specific 5-year survival for Chinese (79.4%) and Filipino (81.4%) cases compared to non-Hispanic whites (77.8%) [22]. The decreased risk of death found among Asian cases may be due to differences in other risk factors associated with cervical cancer outcomes, such as smoking and oral contraceptive use. It has been

hypothesized that oral contraceptives may affect the likelihood of clearance or persistence of HPV infection. It may also affect the regression or progression of pre-neoplastic and neoplastic lesions [23]. The use of oral contraceptive varies greatly among women in the U.S. compared to those in the Asian countries examined in our study. A study examining hormonal contraceptive use among women tested for the presence of oncogenic HPV at clinical centers in the U.S. found that about 58% of women ever reported use of oral contraceptives [24]. In comparison, a study examining oral contraceptive use and HPV reported that 1.1% of Indian women and 3.2% of Chinese women reported ever using oral contraceptives among women tested for infection [25]. Thus, this variation in oral contraceptive use and differences in prevalence of smoking as discussed previously may contribute to favorable cervical cancer survival outcomes found among Asian women.

The stage-specific survival analysis for liver cancer did not produce significant effect estimates for South Asians in our study. However, significantly decreased risk of death was found for Chinese cases at both early and late stage. In addition, decreased risk (HR=0.89; 95% CI 0.84, 0.95) of death was also found for foreign-born cases diagnosed at early stage compared to U.S-born cases. Our findings are generally consistent with several previous studies conducted in the U.S. which have reported more favorable survival among the Asian/Pacific Islander racial/ethnic category compared to non-Hispanic whites [3, 26]. Another recent study reported that among cases diagnosed between 1992 and 2004, Asians/Pacific Islanders consistently had higher one-year survival compared to whites [27]. These differences in survival outcomes may be

associated with the underlying etiology of hepatocellular carcinoma in the U.S. compared to that of the Asian countries examined in our study. A study which reported population attributable fractions (PAF) characterizing the impact of co-morbid conditions on risk of hepatocellular carcinoma in the U.S. reported varying PAF's between whites and Asians for the well-known risk factors. Among whites, the greatest PAF (38.9%) was found for diabetes and/or obesity, while among Asians the highest PAF (43.9%) was associated with HCV infection and alcohol use [28]. Thus, more favorable outcomes may be associated with risk factors found among Asian liver cancer patients compared to those found among non-Hispanic whites.

Due to limited sample sizes, our study did not find significant effect estimates for South Asians in the stage-specific survival analysis for stomach cancer. However, significant decreased risk of death was found for Chinese patients at both early and late stages. In addition, foreign-born cases had significant decreased risk of death compared to those that were U.S.-born at both early (HR=0.77; 95% CI 0.71, 0.83) and late (HR=0.88; 95% CI 0.85, 0.92) stages. Further analysis of gastric cancer subsite revealed that cardia tumors were associated with increased risk of death compared to non-cardia tumors. In our sample, cardia tumors were diagnosed in 35.3% of the non-Hispanic white subjects while the proportions of these tumors ranged from 10.5% to 21.6% in the Asian subpopulations. As mentioned previously, since tumors located in the cardia are associated with poorer prognosis compared to those in non-cardia regions, the greater distribution of the former among non-Hispanic whites may explain the decreased risk of death found among the Asian subpopulations. It has been previously proposed that

countries reporting higher incidence rates of stomach cancer also have more favorable survival compared to countries with lower incidence rates. This finding is also attributed to the differences in survival associated with tumor subsite since gastric cardia tumors are associated with decreased 5-year survival and higher risk of operative mortality. In addition, host-related factors play a role in survival differences since it has been reported that stomach cancers diagnosed among those of Asian origin have better prognosis when compared with non-Asians [10].

A strength of this study is that it is one of the few studies focusing specifically on South Asians and their outcomes for these infection-associated cancers in the U.S. Most studies to date focusing on these cancers have focused on incidence and mortality rates among Asian subpopulations or the Asian/Pacific Islander racial/ethnic group as a whole. Though the estimates were non-significant, heterogeneity of odds ratios among the Asian subpopulations was observed when examining risk of late stage liver cancer. Notable heterogeneity in hazard ratios was also observed among those diagnosed at early stages of both liver and stomach cancers. Thus, our results highlight the need for individual examination of these subpopulations when examining outcomes associated with these infection-associated cancers.

To our knowledge, this is one of the few studies to also examine place of birth as an independent risk factor for outcomes associated with these infection-associated cancers among Asians using SEER in the U.S. Significant effect estimates were obtained for this covariate in the majority of the Cox regression models examining stage-specific survival.

Thus, it is a significant indicator of outcomes associated with infection-associated cancers. Our findings are indicative of certain dietary and other environmental exposures which are associated with more favorable outcomes among patients that are foreign-born compared to those that are U.S.-born.

One limitation of our study is the lack of data regarding the etiology and risk factors related to the infection-associated cancers examined. There are likely significant differences in prevalence of risk factors such as HPV infection, tobacco and alcohol use, viral hepatitis infection, and *H. pylori* infection among the Asian subpopulations and non-Hispanic whites. These factors likely play a role in the differing outcomes observed in our analyses. Another limitation is the exclusion of cases with unknown place of birth data since the effect of this covariate was of significant interest in our study. However, inclusion of cases with known place of birth did not significantly affect the effect estimates obtained in our analyses. Misclassification of our main exposure of interest, race/ethnicity, was also possible. However, a recent study examining the accuracy this variable among the Asian subpopulations used in our study in a SEER registry in California reported that this misclassification is not a significant issue [29]. Our study also had small sample sizes for the South Asian cases in particular for all of the cancers examined. This is due to limited SEER coverage of the Asian population. A recent study reported that SEER only covers 53% of the Asian population in the U.S [30]. However, SEER is currently the only population-based source of data for examining cancer burden in the U.S.

Conclusion

Our study findings indicate that certain Asian subpopulations examined in our analyses had more favorable outcomes related to stage at diagnosis and stage-specific survival when compared to non-Hispanic whites. However, future research should specifically examine these outcomes in South Asian patients in the U.S. Due to limited sample size, the effect estimates for this significant Asian subpopulation in the U.S. obtained in our analyses did not achieve statistical significance. However, South Asians had the highest proportion of late stage liver cancer cases in our study. Recent studies have suggested that this group may have certain risk factors, such as high diabetes prevalence, associated with negative outcomes related to liver cancer. This needs to be examined further in order to tailor cancer prevention programs to this specific subpopulation. In addition, SEER coverage of the Asian population in the U.S. must be more sufficient to achieve accurate estimates of the cancer burden among this major racial/ethnic group.

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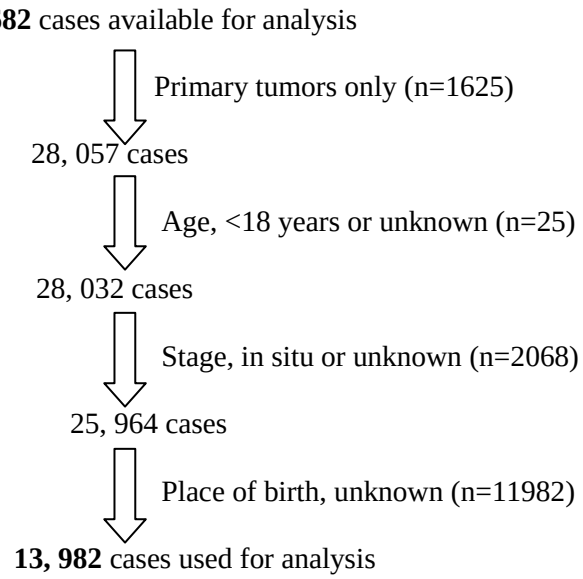
2.7. Tables and Figures

Figure 2-1: Exclusions used to create final analytic samples for analysis

Cervical cancer



Liver cancer

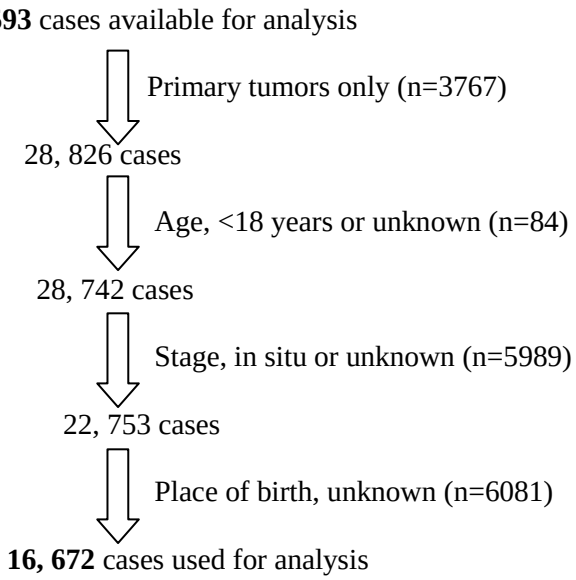


Figure 2-1 (continued)
Stomach cancer

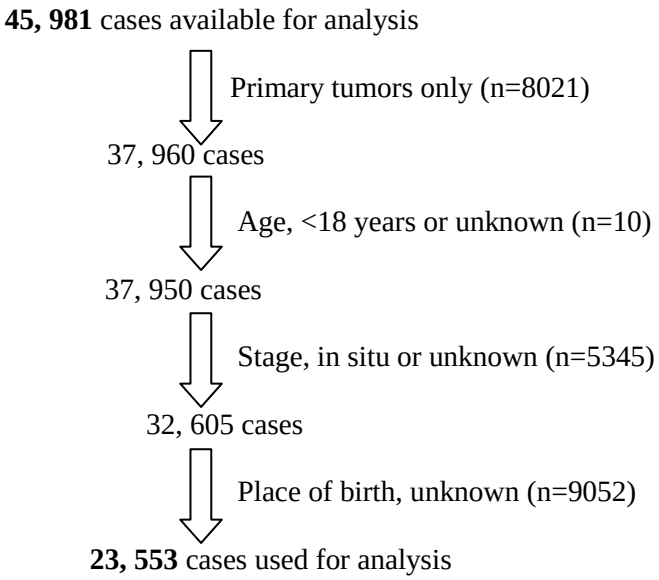


Table 2-1: Demographic and tumor characteristics among 13, 982 cases diagnosed with primary cervical cancer by race, 1999-2009

Characteristic	Asian (n=950)	Non-Hispanic White (n=13, 032)	*P-value
Age at diagnosis (years)			
Mean ± SD	54 ± 15	51 ± 15	
Year of diagnosis			
1999-2001	234 (24.6)	3578 (27.5)	0.204
2002-2004	282 (29.7)	3833 (29.4)	
2005-2007	262 (27.6)	3500 (26.9)	
2008-2009	172 (18.1)	2121 (16.3)	
SEER registry			
San Francisco-Oakland	112 (11.8)	391 (3.0)	<.0001
Los Angeles	309 (32.5)	3057 (23.5)	
San Jose-Monterey	46 (4.8)	320 (2.5)	
Greater California	10 (1.1)	960 (7.4)	
Connecticut	9 (1.0)	670 (5.1)	
Detroit	5 (0.5)	384 (3.0)	
Hawaii	146 (15.4)	83 (0.6)	
Iowa	7 (0.7)	395 (3.0)	
New Mexico	0 (0.0)	226 (1.7)	
Seattle-Puget Sound	53 (5.6)	580 (4.5)	
Utah	1 (0.1)	190 (1.5)	
Atlanta	16 (1.7)	337 (2.6)	
Greater Georgia	189 (19.9)	3128 (24.0)	
Rural Georgia	0 (0.0)	23 (0.2)	
Kentucky	1 (0.1)	524 (4.0)	
Louisiana	1 (0.1)	424 (3.3)	
New Jersey	45 (4.7)	1340 (10.3)	
Stage at diagnosis			
Early	461 (48.5)	6291 (48.3)	0.880
Late	489 (51.5)	6741 (51.7)	
Grade			
I	82 (8.6)	1050 (8.1)	0.600
II	268 (28.2)	3844 (29.5)	
III	302 (31.8)	4213 (32.3)	
IV	24 (2.5)	397 (3.1)	
Unknown	274 (28.8)	3528 (27.1)	
Place of birth			
U.S-born	151 (15.9)	8852 (67.9)	<.0001
Foreign-born	799 (84.1)	4180 (32.1)	

* P-values based on the χ^2 test

Table 2-2: Demographic and tumor characteristics among 16, 672 cases diagnosed with primary hepatocellular carcinoma by race, 1999-2009

Characteristic	South Asian (n=73)	Chinese (n=1130)	Japanese (n=464)	Filipino (n=729)	Non-Hispanic White (n=14,276)	*P-value
Age at diagnosis, y						
Mean ± SD	62 ± 11	63 ± 13	68 ± 11	63 ± 13	63 ± 12	
Sex						
Male	56 (76.7)	857 (75.8)	241 (51.9)	558 (76.5)	11024 (77.2)	<.0001
Female	17 (23.3)	273 (24.2)	223 (48.1)	171 (23.5)	3252 (22.8)	
Year of diagnosis						
1999-2001	12 (16.4)	251 (22.2)	105 (22.6)	161 (22.1)	2763 (19.4)	<.0001
2002-2004	20 (27.4)	334 (29.6)	152 (32.8)	195 (26.8)	3749 (26.3)	
2005-2007	20 (27.4)	330 (29.2)	123 (26.5)	245 (33.6)	4504 (31.6)	
2008-2009	21 (28.8)	215 (19.0)	84 (18.1)	128 (17.6)	3260 (22.8)	
SEER registry						
San Francisco-Oakland	3 (4.1)	343 (30.4)	28 (6.0)	133 (18.2)	578 (4.1)	<.0001
Los Angeles	3 (4.1)	355 (31.4)	80 (17.2)	174 (23.9)	2101 (14.7)	
San Jose-Monterey	2 (2.7)	79 (7.0)	14 (3.0)	40 (5.5)	339 (2.4)	
Greater California	0 (0.0)	5 (0.4)	0 (0.0)	0 (0.0)	809 (5.7)	
Connecticut	4 (5.5)	11 (1.0)	4 (0.9)	5 (0.7)	805 (5.6)	
Detroit	10 (13.7)	14 (1.2)	4 (0.9)	8 (1.1)	790 (5.5)	
Hawaii	0 (0.0)	70 (6.2)	210 (45.3)	113 (15.5)	122 (0.9)	
Iowa	0 (0.0)	4 (0.4)	1 (0.2)	1 (0.1)	537 (3.8)	
New Mexico	1 (1.4)	1 (0.1)	1 (0.2)	1 (0.1)	453 (3.2)	
Seattle-Puget Sound	7 (9.6)	71 (6.3)	30 (6.5)	34 (4.7)	1000 (7.0)	
Utah	1 (1.4)	2 (0.2)	4 (0.9)	1 (0.1)	245 (1.7)	
Atlanta	6 (8.2)	7 (0.6)	1 (0.2)	0 (0.0)	288 (2.0)	
Greater Georgia	2 (2.7)	120 (10.6)	83 (17.9)	189 (25.9)	3481 (24.4)	
Rural Georgia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	25 (0.2)	
Kentucky	0 (0.0)	3 (0.3)	0 (0.0)	0 (0.0)	591 (4.1)	
Louisiana	1 (1.4)	4 (0.4)	1 (0.2)	3 (0.4)	716 (5.0)	
New Jersey	33 (45.2)	41 (3.6)	3 (0.7)	27 (3.7)	1396 (9.8)	

Table 2-2 (continued)

Stage at diagnosis						
Early	38 (52.0)	745 (65.9)	312 (67.2)	419 (57.5)	8574 (60.1)	<.0001
Late	35 (48.0)	385 (34.1)	152 (32.8)	310 (42.5)	5702 (39.9)	
Grade						
I	8 (11.0)	135 (12.0)	67 (14.4)	88 (12.1)	1904 (13.3)	0.037
II	14 (19.2)	200 (17.7)	79 (17.0)	133 (18.2)	2256 (15.8)	
III	8 (11.0)	112 (9.9)	49 (10.6)	96 (13.2)	1294 (9.1)	
IV	1 (1.4)	9 (0.8)	5 (1.1)	7 (1.0)	155 (1.1)	
Unknown	42 (57.5)	674 (59.7)	264 (56.9)	405 (55.6)	8667 (60.7)	
Place of birth						
U.S-born	3 (4.1)	68 (6.0)	248 (53.5)	77 (10.6)	11574 (81.1)	<.0001
Foreign-born	70 (95.9)	1062 (94.0)	216 (46.5)	652 (89.4)	2702 (18.9)	

* P-values based on the χ^2 test

Table 2-3: Demographic and tumor characteristics among 23, 553 cases diagnosed with primary gastric adenocarcinoma by race, 1999-2009

Characteristic	South Asian (n=97)	Chinese (n=883)	Japanese (n=1055)	Filipino (n=496)	Non-Hispanic White (n=21, 022)	*P-value
Age at diagnosis, y						
Mean ± SD	62 ± 15	68 ± 15	73 ± 12	68 ± 14	67 ± 14	
Sex						
Male	63 (65.0)	513 (58.1)	581 (55.1)	258 (52.0)	13631 (64.8)	<.0001
Female	34 (35.0)	370 (41.9)	474 (44.9)	238 (48.0)	7391 (35.2)	
Year of diagnosis						
1999-2001	14 (14.4)	230 (26.1)	358 (33.9)	113 (22.8)	5543 (26.4)	<.0001
2002-2004	37 (38.1)	252 (28.5)	313 (29.7)	159 (32.1)	6348 (30.2)	
2005-2007	25 (25.8)	224 (25.4)	258 (24.5)	133 (26.8)	5672 (27.0)	
2008-2009	21 (21.7)	177 (20.1)	126 (11.9)	91 (18.4)	3459 (16.5)	
Stage at diagnosis						
Early	28 (28.9)	318 (36.0)	393 (37.2)	157 (31.7)	6662 (31.7)	0.0003
Late	69 (71.1)	565 (64.0)	662 (62.8)	339 (68.3)	14360 (68.3)	
SEER registry						
San Francisco-Oakland	8 (8.3)	223 (25.3)	48 (4.6)	64 (12.9)	684 (3.3)	<.0001
Los Angeles	1 (1.0)	287 (32.5)	219 (20.8)	99 (20.0)	3103 (14.8)	
San Jose-Monterey	2 (2.1)	57 (6.5)	27 (2.6)	25 (5.0)	400 (1.9)	
Greater California	1 (1.0)	4 (0.5)	3 (0.3)	1 (0.2)	1043 (5.0)	
Connecticut	1 (1.0)	9 (1.0)	4 (0.4)	4 (0.8)	1786 (8.5)	
Detroit	15 (15.5)	6 (0.7)	2 (0.2)	5 (1.0)	1356 (6.5)	
Hawaii	2 (2.1)	69 (7.8)	565 (53.6)	114 (23.0)	153 (0.7)	
Iowa	1 (1.0)	1 (0.1)	1 (0.1)	0 (0.0)	1028 (4.9)	
New Mexico	0 (0.0)	1 (0.1)	1 (0.1)	0 (0.0)	575 (2.7)	
Seattle-Puget Sound	8 (8.3)	51 (5.8)	52 (4.9)	29 (5.9)	1290 (6.1)	
Utah	0 (0.0)	0 (0.0)	6 (0.6)	1 (0.2)	457 (2.2)	
Atlanta	8 (8.3)	15 (1.7)	4 (0.4)	0 (0.0)	418 (2.0)	
Greater Georgia	2 (2.1)	94 (10.7)	110 (10.4)	126 (25.4)	3724 (17.7)	
Rural Georgia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	38 (0.2)	

Table 2-3 (continued)

Kentucky	0 (0.0)	1 (0.1)	4 (0.4)	0 (0.0)	937 (4.5)	
Louisiana	1 (1.0)	7 (0.8)	1 (0.1)	3 (0.6)	860 (4.1)	
New Jersey	47 (48.5)	58 (6.6)	8 (0.8)	25 (5.0)	3170 (15.1)	
Grade						
I	3 (3.1)	25 (2.8)	44 (4.2)	10 (2.0)	677 (3.2)	<.0001
II	28 (28.9)	156 (17.7)	235 (22.3)	94 (19.0)	4533 (21.6)	
III	55 (56.7)	577 (65.4)	665 (63.0)	323 (65.1)	12124 (57.7)	
IV	1 (1.0)	23 (2.6)	16 (1.5)	6 (1.2)	455 (2.2)	
Unknown	10 (10.3)	102 (11.6)	95 (9.0)	63 (12.7)	3233 (15.4)	
Tumor subsite						
Cardia	21 (21.6)	93 (10.5)	138 (13.1)	79 (15.9)	7421 (35.3)	<.0001
Non-cardia	50 (51.5)	587 (66.5)	663 (62.8)	285 (57.5)	8649 (41.1)	
Overlapping/NOS	26 (26.8)	203 (23.0)	254 (24.1)	132 (26.6)	4952 (23.6)	
Place of birth						
U.S-born	4 (4.1)	61 (6.9)	722 (68.4)	63 (12.7)	15319 (72.9)	<.0001
Foreign-born	93 (95.9)	822 (93.1)	333 (31.6)	433 (87.3)	5703 (27.1)	

* P-values based on the χ^2 test

Table 2-4: Risk of late stage cervical cancer diagnosis by race, 1999-2009 (n=13, 982)

Race	**Age-adjusted model (Race, age, and place of birth only)** OR (95% CI)	***Fully adjusted model** OR (95% CI)
White	1.00 (Referent)	1.00 (Referent)
Asian	1.02 (0.89, 1.18)	1.09 (0.94, 1.26)
Place of birth (all subjects)		
U.S.-born	1.00 (Referent)	1.00 (Referent)
Foreign-born	0.79 (0.73, 0.85)	0.92 (0.84, 1.00)
Place of birth (Asians only)		
U.S.-born	1.00 (Referent)	1.00 (Referent)
Foreign-born	1.11 (0.76, 1.62)	1.02 (0.66, 1.59)

*Adjusted for age at diagnosis, year of diagnosis, SEER registry, and place of birth

Table 2-5: Risk of late stage liver cancer diagnosis by race, 1999-2009 (n=16, 672)

Race	**Age-adjusted model (Race age, and place of birth only)** OR (95% CI)	***Fully adjusted model** OR (95% CI)
White	1.00 (Referent)	1.00 (Referent)
South Asian	1.45 (0.91, 2.30)	1.28 (0.80, 2.05)
Chinese	0.79 (0.69, 0.91)	0.88 (0.75, 1.02)
Japanese	0.74 (0.61, 0.90)	0.91 (0.73, 1.14)
Filipino	1.14 (0.97, 1.34)	1.25 (1.05, 1.48)
Place of birth (all subjects)		
U.S.-born	1.00 (Referent)	1.00 (Referent)
Foreign-born	0.95 (0.88, 1.03)	1.02 (0.94, 1.11)
Place of birth (Asians only)		
U.S.-born	1.00 (Referent)	1.00 (Referent)
Foreign-born	1.01 (0.78, 1.31)	1.03 (0.77, 1.38)

*Adjusted for age at diagnosis, sex, year of diagnosis, SEER registry, and place of birth

Table 2-6: Risk of late stage stomach cancer diagnosis by race, 1999-2009 (n=23, 553)

Race	**Age-adjusted model (Race, age, and place of birth only)** OR (95% CI)	***Fully adjusted model** OR (95% CI)
White	1.00 (Referent)	1.00 (Referent)
South Asian	0.97 (0.62, 1.52)	0.96 (0.61, 1.52)
Chinese	0.81 (0.70, 0.94)	0.81 (0.69, 0.95)
Japanese	0.91 (0.80, 1.03)	0.84 (0.71, 0.99)
Filipino	1.00 (0.82, 1.22)	0.98 (0.80, 1.20)
Place of birth (all subjects)		
U.S.-born	1.00 (Referent)	1.00 (Referent)
Foreign-born	1.05 (0.98, 1.12)	1.08 (1.00, 1.16)
Place of birth (Asians only)		
U.S.-born	1.00 (Referent)	1.00 (Referent)
Foreign-born	0.93 (0.74, 1.16)	0.95 (0.73, 1.24)

*Adjusted for age at diagnosis, sex, year of diagnosis, SEER registry, and place of birth

Table 2-7: Cervical cancer stage-specific survival by race, 1999-2009 (n=13, 982)

Race	**Age-adjusted model (Race and age only)** HR (95% CI)	***Fully adjusted model** HR (95% CI)
Early stage (IA-IIA)		
White	1.00 (Referent)	1.00 (Referent)
Asian	0.57 (0.44, 0.72)	0.82 (0.63, 1.06)
Late stage (>IIA)		
White	1.00 (Referent)	1.00 (Referent)
Asian	0.63 (0.55, 0.72)	0.76 (0.65, 0.87)

Race	**Age-adjusted model (Race, place of birth, and age only)** HR (95% CI)	****Fully adjusted model** HR (95% CI)
Early stage (IA-IIA)		
White	1.00 (Referent)	1.00 (Referent)
Asian	0.80 (0.62, 1.02)	0.94 (0.72, 1.23)
Place of birth		
U.S. born	1.00 (Referent)	1.00 (Referent)
Foreign	0.51 (0.45, 0.58)	0.76 (0.66, 0.88)
Late stage (>IIA)		
White	1.00 (Referent)	1.00 (Referent)
Asian	0.88 (0.77, 1.01)	0.94 (0.81, 1.10)
Place of birth		
U.S. born	1.00 (Referent)	1.00 (Referent)
Foreign born	0.55 (0.51, 0.59)	0.66 (0.61, 0.72)

*Adjusted for age at diagnosis, SEER registry, and grade
**Adjusted for age at diagnosis, SEER registry, grade, and place of birth

Table 2-8: Liver cancer stage-specific survival by race, 1999-2009 (n=16, 672)

Race	**Age-adjusted model (Race, age, and place of birth only)** HR (95% CI)	***Fully adjusted model** HR (95% CI)
Early stage (I/II)		
White	1.00 (Referent)	1.00 (Referent)
South Asian	1.28 (0.88, 1.87)	1.03 (0.70, 1.50)
Chinese	0.64 (0.57, 0.71)	0.69 (0.62, 0.78)
Japanese	0.77 (0.67, 0.88)	0.84 (0.72, 0.98)
Filipino	1.02 (0.90, 1.15)	1.13 (0.99, 1.29)
Place of birth		
U.S.-born	1.00 (Referent)	1.00 (Referent)
Foreign-born	0.80 (0.75, 0.85)	0.89 (0.84, 0.95)
Late stage (III/IV)		
White	1.00 (Referent)	1.00 (Referent)
South Asian	1.09 (0.75, 1.58)	1.06 (0.73, 1.54)
Chinese	0.77 (0.68, 0.87)	0.79 (0.70, 0.90)
Japanese	0.90 (0.76, 1.07)	0.89 (0.73, 1.08)
Filipino	0.87 (0.76, 1.00)	0.90 (0.78, 1.03)
Place of birth		
U.S.- born	1.00 (Referent)	1.00 (Referent)
Foreign-born	0.97 (0.91, 1.04)	1.03 (0.96, 1.11)

*Adjusted for age at diagnosis, sex, SEER registry, grade, and place of birth

Table 2-9: Stomach cancer stage-specific survival by race, 1999-2009 (n=23, 553)

Race	**Age-adjusted model (Race, age, and place of birth only)** HR (95% CI)	***Fully adjusted model** HR (95% CI)
Early stage (I/II)		
White	1.00 (Referent)	1.00 (Referent)
South Asian	1.65 (0.99, 2.75)	1.39 (0.83, 2.32)
Chinese	0.59 (0.49, 0.71)	0.65 (0.53, 0.79)
Japanese	0.66 (0.58, 0.76)	0.87 (0.73, 1.04)
Filipino	0.94 (0.76, 1.16)	1.02 (0.82, 1.28)
Place of birth		
U.S. born	1.00 (Referent)	1.00 (Referent)
Foreign	0.64 (0.60, 0.69)	0.77 (0.71, 0.83)
Late stage (III/IV)		
White	1.00 (Referent)	1.00 (Referent)
South Asian	0.87 (0.67, 1.13)	0.87 (0.67, 1.12)
Chinese	0.77 (0.70, 0.85)	0.80 (0.72, 0.89)
Japanese	0.75 (0.69, 0.82)	0.77 (0.69, 0.85)
Filipino	0.91 (0.81, 1.03)	0.91 (0.80, 1.03)
Place of birth		
U.S. born	1.00 (Referent)	1.00 (Referent)
Foreign born	0.83 (0.80, 0.87)	0.88 (0.85, 0.92)

*Adjusted for age at diagnosis, sex, SEER registry, grade, and place of birth

Table 2-10: Effect of place of birth on stomach cancer stage-specific survival by subsite

		***HR (95% CI)**
Cardia		
Early stage	U.S.-born	1.00 (Referent)
	Foreign born	0.87 (0.74, 1.03)
Late stage	U.S.-born	1.00 (Referent)
	Foreign born	0.89 (0.81, 0.98)
Non-cardia		
Early stage	U.S.-born	1.00 (Referent)
	Foreign born	0.76 (0.68, 0.84)
Late stage	U.S.-born	1.00 (Referent)
	Foreign born	0.89 (0.83, 0.95)

*Adjusted for age at diagnosis, sex, SEER registry, and grade

3. BREAST CANCER STAGE AT DIAGNOSIS AND STAGE-SPECIFIC SURVIVAL AMONG SOUTH ASIANS AND OTHER ASIAN SUBPOPULATIONS IN THE UNITED STATES

3.1 Abstract

Asian subpopulations living in the United States are heterogeneous with regard to time since immigration and acculturation. Both of these factors likely play a significant role in explaining varying breast cancer outcomes among these groups. Despite being the third largest Asian subpopulation in the U.S., South Asians comprise a group whose cancer outcomes have not been well examined and documented in the literature. We utilized data from the Surveillance, Epidemiology, and End Results (SEER) program to examine differences in breast cancer stage at diagnosis and stage-specific survival among South Asian women and other Asian (Chinese, Japanese, Filipino) women compared to non-Hispanic white women in the U.S. Logistic regression was utilized to examine the association between South Asian race and breast cancer stage at diagnosis. Stage-specific survival following breast cancer diagnosis was also examined among the racial groups of interest using proportional hazards models. Among the Asian subpopulations, the highest risk for late stage diagnosis of breast cancer when compared to non-Hispanic whites was found among South Asians. Though non-significant, the adjusted model which also accounted for place of birth found 3% (OR=0.97; 95% CI 0.81, 1.16) reduced risk for late stage diagnosis for this group compared to non-Hispanic whites. South Asian women had the most favorable stage-specific survival for both early and late stage diagnosis among the other Asian subpopulations when compared to non-Hispanic whites. The adjusted model which also accounted for place of birth showed that among those

diagnosed with early-stage disease, South Asians had 39% significant reduced risk (95% CI 0.44, 0.84) of death when compared to non-Hispanic whites. Among those diagnosed with late-stage disease, this group had 20% reduced risk (95% CI 0.59, 1.09) of death when compared to non-Hispanic whites. Our findings revealed that South Asians were more likely to present with advanced stage at diagnosis compared to the other Asian subpopulations we examined. This may be attributable to genetic differences which are associated with the more aggressive features common for tumors diagnosed among South Asian women. There are also likely differences in health-seeking behaviors which exist among these groups. Our findings highlight a true need for more individualized prevention methods for South Asians in the U.S. in order to improve outcomes associated with breast cancer.

3.2. Background

Breast cancer is the most common cancer and the second leading cause of death attributable to cancer among women in the United States [1]. There are currently approximately three million women in the U.S. who have been diagnosed with invasive breast cancer [2]. Breast cancer incidence varies across countries due to factors such as racial/ethnic differences in genetics, reproductive behaviors, and lifestyle exposures such as diet which differ across countries [3].

When examining Asians living in the U.S., it has been found that these populations are heterogeneous with regard to time since immigration and acculturation. Both of these factors likely play a significant role in explaining varying breast cancer outcomes among these groups [4]. Several previous studies have shown differences in breast cancer incidence rates among Asian subpopulations in the U.S [5-13]. However, few have examined differences in outcomes such as stage at diagnosis and stage-specific survival. It has been reported that when assessed collectively, Asian/Pacific Islander women do not differ greatly from non-Hispanic whites when examining stage at diagnosis and overall survival. However, variations in these outcomes may be observed when examining the individual groups that comprise this aggregate population [14].

Despite being the third largest Asian subpopulation in the U.S. [15], South Asians comprise a group whose cancer outcomes have not been well examined and documented in the literature [6]. Studies examining breast cancer outcomes, such as stage at diagnosis and stage-specific survival, among South Asians residing in the U.S. are limited. A study

published in 2003 examining breast cancers diagnosed among Asian subpopulations in the U.S. between 1992 and 1998 reported that South Asians were at increased risk of late stage diagnosis but had more favorable survival compared to non-Hispanic whites [14]. We aim to extend on these findings by also examining the association of place of birth with these outcomes. It has been previously reported that though South Asians are generally of higher socioeconomic status compared to other Asian subpopulations, adherence to breast cancer screening guidelines is relatively low. This is especially true among recent immigrants to the U.S. The majority of studies reporting on the breast cancer burden in this predominant Asian subpopulation have been conducted overseas. Thus, the findings of these studies cannot be generalized to South Asians living in the U.S since factors such as diet and reproductive behaviors, which are known to be associated with breast cancer outcomes, likely vary between countries [5].

In order to better understand and address the breast cancer burden on the South Asian population in the U.S., this study will examine this racial/ethnic group separately from the other predominant Asian subpopulations in the country. Through use of data from the Surveillance, Epidemiology, and End Results (SEER) program of the National Cancer Institute (NCI), we aim to examine differences in breast cancer stage at diagnosis and stage-specific survival among South Asian women and other Asian (Chinese, Japanese, Filipino) women compared to non-Hispanic white women in the U.S.

3.3. Methods

Our study population included all women identified as South Asian, Chinese, Japanese, Filipino, or non-Hispanic white diagnosed with incident primary invasive breast cancer between January 1, 1999 and December 31, 2009 among 17 population-based cancer registries included in the SEER program. South Asian is defined in our study as those originating from either India or Pakistan as classified by SEER. Since 1988, these two countries of origin have been combined to create one racial/ethnic category in SEER. The following registries were included in our analyses: San Francisco-Oakland, Los Angeles, San Jose-Monterey, Greater California, Connecticut, Detroit, Hawaii, Iowa, New Mexico, Seattle- Puget Sound, Utah, Atlanta, Greater Georgia, Rural Georgia, Kentucky, Louisiana, and New Jersey. Patient data were ascertained by SEER from medical records and available information for each diagnosed case included demographics, tumor characteristics at diagnosis, and year of diagnosis.

A total of 616,156 female breast cancer cases belonging to our subpopulations of interest were available for analysis. We first excluded women whose primary diagnosis was not breast cancer (n=190,132). Those less than 18 years at diagnosis or with unknown age at diagnosis were also excluded (n=29). In addition, those with in situ or unknown stage at diagnosis were also excluded (n=24,674). We examined place of birth as a variable of interest in our study. Subjects were classified as either “U.S.-born” or “foreign-born” based on data extracted by SEER from patient medical records or death certificates. Since one principal aim of this study was to make inferences regarding the effect of U.S. versus foreign birth on subsequent breast cancer outcomes, those with unknown place of

birth were excluded from our analyses (n=217,775). Demographic and tumor characteristics of the eligible Asian cases prior to these exclusions are shown in **Appendix C**. A total of 183,546 women met these inclusion criteria and were included in our analytic sample.

Several covariates were considered to be potential confounders in our analyses. The models used in the logistic regression analysis adjusted for the effects of age at diagnosis, year of diagnosis, and SEER registry. Age is adjusted for as a confounder due to its varying distributions in the racial/ethnic subgroups examined and due to the association between older age and increased risk of cancer. Year of diagnosis is taken into account since diagnosis and surveillance methods for cancer detection may have varied during the time period of our study. SEER registry is adjusted for to take into account the location from which the cases originated since access to care and likelihood of diagnosis may vary between locations. The models used in the survival analysis also adjusted for the effects of grade, ER status, and PR status in addition to the covariates used in the logistic regression analysis. These tumor characteristics are taken into account due to their effect on survival. In addition, these characteristics may vary due to genetic differences between the racial/ethnic subgroups being compared.

The primary association of interest in the logistic regression analysis was the effect of South Asian race on breast cancer stage at diagnosis. Subjects were categorized as having early (I or II) or late (III or IV) stage disease using AJCC staging, with the outcome of interest defined as late stage at diagnosis. Logistic regression was conducted

to obtain odds ratios and 95% confidence intervals to examine the association between race and late stage at diagnosis while controlling for potential confounding by age at diagnosis, year of diagnosis, and SEER registry. Age-adjusted associations were first obtained using models with only race and age as predictors. Adjusted associations were then examined which controlled for potential confounders. We also examined the effect of place of birth by including it as a predictor along with race and the other covariates. Non-Hispanic whites served as the referent racial group in all models.

We also examined potential interactions between race and place of birth. All Asians were combined to create one category and compared to the reference group of non-Hispanic whites in a crude model which included Asian race, place of birth, and the interaction of these covariates. An aggregate categorical indicator for Asian race was used due to the small sample sizes found when examining the individual subpopulations separately. Place of birth was categorized as U.S or foreign-born with the U.S.-born cases serving as the reference group.

Stage-specific survival following breast cancer diagnosis was also examined among the racial groups of interest. Survival time was provided as a variable in the SEER database and was calculated by using the date of diagnosis and the earliest of the following: date of death, date last known to be alive, or the follow-up cutoff date of December 31, 2009. In addition, vital status was provided in the data as either “alive” or “dead.” The Kaplan-Meier method was utilized to detect significant differences in overall survival between the racial groups being compared through use of the log-rank test. Cox proportional

hazards regression was utilized for multivariate adjustment to assess the effects of age, SEER registry, stage, grade, estrogen receptor (ER) status, and progesterone receptor (PR) status on the observed racial differences in survival. The proportional hazards (PH) assumption was assessed for these covariates prior to inclusion in the models through use of log-log plots and assessment of time-varying covariates. Violation of the PH assumption was observed for stage and age, resulting in stratification by stage and inclusion of a time-varying covariate for age. In addition, non-parallelism in the graphical test of the PH assumption for ER status, PR status, and grade resulted in exclusion of cases in the unknown categories of these variables. Hazard ratios and 95% confidence intervals were obtained to examine the association between race and stage-specific survival. Age-adjusted associations were obtained using models with only race and age as predictors. Adjusted estimates were then examined which controlled for potential confounders. We also examined the effect of place of birth by including it as a predictor along with race and the other covariates. All analyses were conducted using SAS, version 9.3 (SAS Institute, Inc., Cary, NC).

3.4. Results

The distribution of demographic and tumor characteristics of interest by race is shown in **Table 3-1**. South Asian women had the highest proportion of diagnosed cases in the youngest age category (18-39 years, 15%) among the racial groups, while Japanese women had the highest proportion in the oldest age category (≥70 years, 36.7%). The majority of South Asian cases were reported from New Jersey while the other Asian groups were reported mostly from registries in California and Hawaii. Non-Hispanic

white cases were also mostly obtained from reporting sites in California. The highest proportions of stage III and IV cancers among the racial groups were found in South Asians while the lowest proportions were in Japanese women. This pattern was also found among tumors diagnosed at grades III and IV. South Asians also had the highest proportions among the racial groups of tumors diagnosed as ER and PR negative. Foreign-born cases were highest among Filipino women, while the lowest proportion was found among Japanese women.

Table 3-2 shows the results obtained from the age-adjusted and fully adjusted logistic regression models examining the association between race and late stage at diagnosis. When examining the age-adjusted model with race and age as the only predictors, South Asians had significantly increased risk (24%) of late stage diagnosis compared to non-Hispanic whites. In comparison, the other Asian groups had significantly decreased risk according to this model. The elevated risk among South Asians became non-significant and reduced to 7% increased risk after adjusting for age at diagnosis, year at diagnosis, and SEER registry. The decreased risk observed among the other Asian groups remained significant in this adjusted model, with the exception of Filipino cases.

Place of birth was also included as a covariate to examine its potential to confound the association between race and late stage at diagnosis. Though it did not achieve statistical significance, the age-adjusted model with race, age, and place of birth as predictors showed that South Asians had increased risk (18%) of late stage diagnosis compared to non-Hispanic whites. The odds ratio estimate obtained for the fully adjusted model showed that the risk was no longer elevated (OR=0.97; 95% CI 0.81, 1.16) after

controlling for the effects of confounders. When examining the independent effect of place birth after adjusting for the other covariates, it was observed that U.S.-born cases had significantly lower risk of late stage at diagnosis compared to those that were foreign-born in all of the models used.

We also assessed the interaction between race and place of birth. The crude model found a significant effect for the interaction term (OR=1.26; 95% CI 1.12, 1.42), suggesting that the association between Asian race and late stage at diagnosis may vary by place of birth. This significant effect estimate for the interaction between race and place of birth indicates that there is an increased risk of late stage diagnosis among Asians who are foreign-born. However, this interaction term was no longer significant when included in the fully adjusted model (OR=0.98; 95% CI 0.86, 1.12). In addition, interaction between individual Asian races and place of birth was also examined. However, these interaction effects were found to be non-significant.

Figure 3-1 shows the proportion of late stage diagnosis by place of birth among the Asian groups examined. The proportion of late stage cases is higher among the foreign-born across the racial groups, with the exception of Japanese cases where the proportion is greater among the U.S.-born cases. South Asian cases had the greatest proportion of late stage diagnoses for both U.S. and foreign-born cases, while the lowest was seen among Japanese cases. The greatest difference in proportion of late stage cases according to place of birth was also seen among the South Asians, although this difference was not statistically significant.

Figure 3-2 show unadjusted Kaplan-Meier curves examining overall survival comparing South Asians to the other Asian groups of interest in our study and non-Hispanic whites. The log-rank test p-value which can be used to detect significant differences in the survival curves is also shown. As can be seen in the figure, South Asians had worse unadjusted overall survival compared to the other Asian groups. However, they had more favorable unadjusted overall survival when compared to non-Hispanic whites. The log-rank test p-value of <.0001 indicates significant difference in the survival curves between the racial/ethnic groups being compared. **Figure 3-3** shows the unadjusted curves of the Asian subpopulations only. The log-rank test p-value of 0.001 shows that significant differences in the survival curves remain after exclusion of non-Hispanic whites.

Figures 3-4 through **3-6** display the distributions of ER status, PR status, and tumor grade among the Asian groups examined. All of these tumor characteristics play a major role in determining outcomes associated with breast cancer. More favorable outcomes are often found when tumors are diagnosed as positive for hormone receptors, such as ER and PR. South Asians had the lowest proportions of both ER and PR positive tumors when compared to the other Asian groups. This group also had the highest proportion of tumors diagnosed at grades III and IV.

The results of the Cox regression analysis examining the association between race and stage-specific survival are shown in **Table 3-3**. Stage-specific survival was examined by conducting the analyses separately among those diagnosed with early (I or II) and late (III or IV) stage breast cancer. When examining the age-adjusted model with only race and

age as predictors, it was found that among those diagnosed with early stage disease, South Asians had significantly decreased risk (HR=0.61; 95% CI 0.44, 0.84) of death compared to non-Hispanic whites. The other Asian groups also had significantly decreased risk of death in this model. This decreased risk of death among South Asians remained significant (HR=0.53; 95% CI 0.38, 0.73) and the protective effect of race was not as strong after adjusting for the potentially confounding effects of age at diagnosis, SEER registry, grade, ER status, and PR status. The lowest risk of death was found among South Asians when compared to non-Hispanic whites. The adjusted model also produced significant hazard ratios for the other Asian groups as well. South Asians also had the lowest risk of death when examining those diagnosed with late stage disease. According to the adjusted model, South Asians had 30% reduced risk (HR=0.70, 95% CI 0.51, 0.94) of death compared to non-Hispanic whites among those diagnosed with late stage disease.

Place of birth was also included as a covariate to examine its effect on the association between race and stage-specific survival. When examining the age-adjusted model with race, age, and place of birth as predictors, it was found that among those diagnosed with early stage disease, South Asians still had reduced risk (HR=0.79; 95% CI 0.57, 1.09) of death compared to non-Hispanic whites. The other Asian groups had significantly decreased risk of death in this model. The decreased risk of death among South Asians became statistically significant (HR=0.61; 95% CI 0.44, 0.84) in the fully adjusted model. This model also found the lowest risk of death among South Asians when compared to non-Hispanic whites. Though non-significant (HR=0.80; 95% CI 0.59,

1.09), South Asians were again found to have the lowest risk of death when examining those diagnosed with late stage disease in the fully adjusted model.

Potential interaction effects between race and place of birth associated with stage-specific survival were also examined in the same method used previously for the logistic regression analysis. The crude model which included the main effects of Asian race and place of birth in addition to their interaction found a significant effect (HR=1.57; 95% CI 1.40, 1.76) for the interaction term. This significant effect estimate for the interaction between Asian race and place of birth indicates that there is an increased risk of death among Asians who are foreign-born. This interaction remained significant in the fully adjusted models among those diagnosed at early (HR=1.29; 95% CI 1.10, 1.50) and late (HR=1.32; 95% CI 1.05, 1.67) stages. In addition, interactions between individual Asian races and place of birth were also examined and found to be highly non-significant.

3.5. Discussion

This study found notable heterogeneity of risk when examining late stage breast cancer diagnosis among South Asians and other Asian subpopulations when compared to non-Hispanic whites. South Asians had the highest risk of late stage diagnosis and most favorable stage-specific survival among the Asian groups when compared to non-Hispanic whites. Controlling for the effects of age at diagnosis, year of diagnosis, and SEER registry did not diminish the heterogeneity of these effects. Heterogeneity of effect estimates was also found among the Asian groups when examining stage-specific

breast cancer survival by race, further highlighting the need for individual assessment of breast cancer burden in this aggregate population.

Among the Asian subpopulations, the highest risk for late stage diagnosis of breast cancer when compared to non-Hispanic whites was found among South Asians. Though non-significant, the adjusted model which also accounted for place of birth found 3% (OR=0.97; 95% CI 0.81, 1.16) reduced risk for late stage diagnosis for this group compared to non-Hispanic whites. However, much lower risk was found among the other Asian groups examined. This increased risk for late stage diagnosis found among South Asians compared to non-Hispanic whites was also observed in an earlier study examining the association between race/ethnicity and breast cancer outcomes [14]. Diagnosis of breast cancer at an advanced stage of disease greatly increases risk of mortality and thus reduces survival time. Risk factors for advanced stage diagnosis include low socioeconomic status, belonging to a racial/ethnic minority group, and foreign birth. Studies among immigrant women in the U.S. have found that they are at increased risk for unfavorable breast cancer outcomes due to limited English language proficiency, insufficient health insurance, and experience barriers to access such as social exclusion. As a result, they are less likely to have sufficient knowledge regarding cancer prevention and thus less likely to receive adequate screening prior to diagnosis of disease [16]. However when examining South Asians, it has been found that this minority population is in fact comprised of the highest educated, highest paid, and best insured immigrants in the U.S. Despite seemingly high socioeconomic status, this group has reported insufficient adherence to breast cancer prevention recommendations, such as

regular screenings. This is especially true among recent immigrants to the U.S [5]. The lack of proper prevention methods likely contributes greatly to the advanced stage presentation of breast cancer found among South Asian women.

Our study further demonstrated that South Asian women were more likely to be diagnosed with tumors different from other Asian subpopulations and non-Hispanic whites with regard to clinical and pathological presentation. This group had the greatest proportion of cases (15%) in the youngest age category of 18-39 years. In addition to having the greatest proportion of cases presenting at stages III and IV (23.4%), these women also had the greatest proportion of tumors at grades III and IV (50.6%). They also presented with the greatest proportion of ER and PR- negative tumors. This is consistent with the findings of Moran et al which also reported that South Asian women were diagnosed with tumors of greater stage, larger size, and higher grade when compared to non-Hispanic whites [5]. A recent review of breast cancer burden among South Asian women found that ER and PR status are reported as positive in only about 20-45% of Indian patients. In addition, the proportion of ER-positive tumors was lower overall among these women compared to those of western countries. Negative hormone receptor status tumors are known to be more aggressive and their growth largely can not be controlled with traditional chemotherapy treatment [17]. These pathological characteristics of advanced stage, grade, and negative hormone receptor status, are all indicative of more aggressive and fast-growing breast tumors and likely play a key role in the greater risk of advanced stage diagnosis found among South Asians compared to other Asian subpopulations.

Our findings also showed that when examining the independent effect of place of birth on late stage at diagnosis, the risk was lower among cases that were U.S.-born compared to those that were foreign-born. In the adjusted model that also accounted for age at diagnosis, year of diagnosis, and SEER registry, it was observed that U.S.-born cases had 13% reduced risk (95% CI 0.84, 0.90) of late stage diagnosis compared to those that were foreign-born. This increased risk found among foreign-born women is likely attributable to several factors, such as length of residency in the U.S, English language proficiency, and cultural beliefs towards screening and other preventive practices. A review of breast cancer screening practices among Asian women in the U.S. found that adequate screening according to established guidelines was not conducted in this group. This lack of preventive care undoubtedly leads to increased risk of late stage diagnosis. It has widely been reported that the Asian population in the U.S. is primarily composed of immigrants, with the majority of them reporting foreign-birth [18]. Thus, they likely have differing cultural beliefs regarding health that will at times negatively impact cancer outcomes. These beliefs may include self-sufficiency and greater emphasis on familial obligations rather than individual health. These behaviors likely contribute to decreased contact with primary care and lack of preventive care, such as regular screenings [4]. It has been found that immigrant South Asian women in particular mistakenly view breast cancer as a disease common only to women from westernized societies and do not believe that they are susceptible to the disease [19]. Thus, interventions which target these racial subpopulations is of great public health importance in order to promote breast cancer awareness and to increase uptake of preventive practices such as regular screenings and

self- examinations which will likely lead to reduced advanced stage diagnosis and poor disease outcomes.

Figure 3-7 is a graphical depiction of all of these factors which likely contribute to the association between race/ethnicity and late stage at diagnosis.

Our findings showed that South Asian women had the most favorable stage-specific survival for both early and late stage diagnosis among the other Asian subpopulations when compared to the referent group of non-Hispanic whites. The adjusted model which also accounted for place of birth showed that among those diagnosed with early-stage disease, South Asians had 39% significant reduced risk (95% CI 0.44, 0.84) of death when compared to non-Hispanic whites. Among those diagnosed with late-stage disease, this group had 20% reduced risk (95% CI 0.59, 1.09) of death when compared to non-Hispanic whites. This finding is consistent with an earlier study which also found a decreased risk (HR=0.80; 95% CI 0.60, 1.50) of death among South Asians compared to non-Hispanic whites [14].

It has been well established that risk factors such as late child bearing age, low parity, consumption of high-fat, high-caloric foods, obesity, and physical inactivity are all associated with decreased survival from breast cancer. These reproductive and lifestyle behaviors are also associated with westernized culture [20]. This finding is consistent with our results which showed that Asian women in our subpopulations of interest had better survival compared to non-Hispanic white women in the U.S. The majority of South Asians in the U.S. today are recent immigrants. Only approximately 9% of Asian Indians and 6% of Pakistanis older than 18 years were born in the U.S. according to the 2000

U.S. census. Most adults that comprise this Asian subpopulation immigrated to the U.S. after 1985. As a result of their recent immigration, the extent of acculturation present in this group is relatively low compared to other immigrant groups in the U.S [6]. Our results showed that this group had the best stage-specific survival among the Asian subpopulations examined. The recency of immigration to the U.S. for the majority of this group is likely an explanation for this finding.

Place of birth may be used as a measure of acculturation. Breast cancer cases that are U.S.-born are thus more likely to demonstrate lifestyle behaviors native to the U.S., such as a diet high in fat intake. Those that were U.S.-born had an increased risk of death compared to those that were foreign born in all of the models used in our analyses. This finding is consistent with previous studies which have reported an association between westernized lifestyles and poor breast cancer survival. The decreased risk of death observed among the foreign-born in our study is likely attributable to differences in lifestyle among those that are Asian immigrants who have not yet fully acculturated to the lifestyle behaviors of those native to the U.S [21]. Foreign-born Asian women in particular have been found to consume less dietary fat, report older age at menarche, have children at younger ages, and also breastfeed at greater rates compared to U.S.-born descendants of immigrant women [4]. All of these factors likely contribute to more favorable breast cancer outcomes among these immigrant women compared to non-Hispanic white women in the U.S.

Figure 3-8 is a graphical depiction of all of these factors which likely contribute to the association between race/ethnicity and overall survival following breast cancer diagnosis.

Both the late stage at diagnosis and stage-specific survival analyses produced adjusted effect estimates that were closer to the null than the crude estimates for all of the Asian subpopulations examined. This shift may be attributable to variations in the distribution of age at diagnosis in these groups. Differences in age likely played a role in the heterogeneity of effect estimates found across the groups examined in our study. As seen in **Table 3-1**, the proportions of cases in each age category notably varied among the Asian subpopulations. This trend may be a reflection of varying genetic differences in etiology and subsequent aggressiveness in tumor progression in these populations.

A strength of this study is that it is one of the few studies focusing on breast cancer outcomes among South Asians in the U.S. To date, most studies focusing on this major Asian subpopulation have been conducted abroad in countries such as the U.K. Numerous studies conducted in the South Asian region have reported findings indicating risk factors for more aggressive disease and subsequent advanced stage at diagnosis in this population, such as higher tumor grade and greater proportions of tumors which are hormone-receptor negative [5]. Thus, it is becoming increasingly important to examine these outcomes in South Asians residing in the U.S. in order to better understand the burden of disease and to create effective interventions which target this major population of immigrants.

The findings of our analyses also highlight the need to examine breast cancer burden in this group independently of other the other Asian subpopulations, especially when focusing on stage at diagnosis. Though non-significant, this specific subpopulation had the highest risk for late stage diagnosis compared to the other Asian groups examined and provides further support for the notion that Asians and Pacific Islanders can not be aggregated into a collective racial/ethnic category in epidemiological studies. The decreased risk of late stage diagnosis found among the other Asian subpopulations examined in our study was not apparent for the South Asians cases. Our findings are indicative of certain health-seeking behaviors present among the South Asian community in particular residing in the U.S. which need to be addressed independently of other Asian subpopulations.

To our knowledge, this study is one of the few to take place of birth into account when examining breast cancer outcomes among Asian subpopulations in the U.S. Stanford et al [8] examined differences in breast cancer incidence among Asian immigrants to the U.S. and their descendants, while Pineda et al [21] previously examined survival among Chinese, Japanese, and Filipino immigrants compared to U.S.-born Asians and Caucasians. Neither of these studies took South Asians into account in their analyses. As mentioned previously, place of birth is a significant indicator of breast cancer outcomes when examining Asians living in the U.S., as it has been found that this racial group is heterogeneous with regard to immigration and acculturation.

A limitation of our study is the exclusion of cases with unknown place of birth data. The proportion of cases with unknown place of birth ranged from 28% among Filipino to 55%

among non-Hispanic whites. It was found that the proportion of late stage diagnosis was slightly higher among those with known (58.4%) place of birth compared to those with unknown (41.6%). The degree of completeness regarding this data is a reflection of the methods used by medical staff when ascertaining personal information from patients. In a study examining completeness of birthplace data in the Greater Bay Area Cancer Registry in California, Gomez et al reported that Asians with unknown place of birth data were more likely to be U.S.-born compared to those with recorded place of birth. Thus, the degree of completeness of this data may be differential according to place of birth if hospital staff choose to selectively inquire about this information if a patient is assumed to be foreign-born. Any possible bias introduced by incompleteness of place of birth data can only be addressed through improving data ascertainment methods at the local hospital level [22].

Another limitation of this study is the possible misclassification of our main exposure of interest, which is race/ethnicity. A recent study [23] examining the accuracy of the race/ethnicity variable in a SEER registry in California used predictive value positive (PV+) and sensitivity to quantify the misclassification of this variable. Among the Asian subpopulations of interest in our study, it was reported that PV+ ranged from 80%-92% and sensitivity ranged from 77%-80%. Thus, there is potential underestimation of subpopulation size in our analyses. Another limitation may be the classification of subjects as “foreign-born” if not born within the U.S. Since place of birth is not reported for every subject, it is not feasible to include specific countries of origin when examining this exposure due to small sample sizes for the Asian subpopulations. Despite these

limitations, SEER is currently the most comprehensive source of data regarding cancer burden among the general population currently available in the U.S.

Conclusion

Through individual examination of the major Asian subpopulations that comprise the aggregate Asian/Pacific Islander racial/ethnic category in the U.S., our findings revealed notable heterogeneity in risk of late stage breast cancer at diagnosis and stage-specific survival. Breast cancer is one of the few cancers that responds effectively to treatment when diagnosed at an early stage. Thus, it is becoming increasingly important to create targeted interventions for groups that may be at higher risk for poor outcomes. It is vital to understand which populations are more likely to present with advanced stages of breast cancer in order to ensure that these groups are utilizing proper prevention and management practices. Our findings revealed that South Asians were more likely to present with advanced stage at diagnosis compared to the other Asian subpopulations we examined. This may be attributable to genetic differences which are associated with the more aggressive features common for tumors diagnosed among South Asian women. There are also likely differences in health-seeking behaviors which exist among these groups. It has been previously reported that only 5% of Asian Indian women complete breast self-examinations on a monthly basis, whereas 23% of Chinese and 51% of Filipino women engage in this preventive behavior [6]. Thus, there is a true need for more individualized prevention for this major immigrant population in the U.S. in order to improve outcomes associated with breast cancer.

3.6. List of References

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3.7. Tables and Figures

Table 3-1: Demographic and tumor characteristics among 183,546 women diagnosed with invasive breast cancer by race, 1999-2009

Characteristic	South Asian (n=698)	Chinese (n=3631)	Japanese (n=3172)	Filipino (n=5792)	Non-Hispanic White (n=170,253)
Age at diagnosis, y					
18-39	105 (15.0)	322 (8.9)	149 (4.7)	387 (6.7)	9233 (5.4)
40-49	188 (26.9)	1052 (29.0)	510 (16.1)	1346 (23.2)	29213 (17.2)
50-59	207 (29.7)	1008 (27.8)	685 (21.6)	1795 (31.0)	39674 (23.3)
60-69	130 (18.6)	602 (16.6)	664 (20.9)	1332 (23.0)	36966 (21.7)
≥70	68 (9.7)	647 (17.8)	1164 (36.7)	932 (16.1)	55167 (32.4)
Year of diagnosis					
1999-2001	137 (19.6)	862 (23.7)	951 (30.0)	1345 (23.2)	47591 (28.0)
2002-2004	176 (25.2)	1046 (28.8)	984 (31.0)	1613 (27.9)	50130 (29.4)
2005-2007	209 (29.9)	1042 (28.7)	787 (24.8)	1746 (30.2)	44711 (26.3)
SEER Registry					
San Francisco-Oakland	30 (4.3)	943 (26.0)	166 (5.2)	850 (14.7)	7584 (4.5)
Los Angeles	27 (3.9)	1237 (34.1)	766 (24.2)	1910 (33.0)	28479 (16.7)
San Jose-Monterey	30 (4.3)	255 (7.0)	100 (3.2)	242 (4.2)	3835 (2.3)
Greater California	37 (5.3)	398 (11.0)	327 (10.3)	1478 (25.5)	40638 (23.9)
Connecticut	61 (8.7)	40 (1.1)	9 (0.3)	31 (0.5)	13502 (7.9)
Detroit	23 (3.3)	13 (0.4)	8 (0.3)	13 (0.2)	4999 (2.9)
Hawaii	3 (0.4)	347 (9.6)	1616 (51.0)	669 (11.6)	1691 (1.0)
New Mexico	3 (0.4)	1 (0.03)	3 (0.1)	3 (0.1)	2992 (1.8)
Seattle-Puget Sound	48 (6.9)	132 (3.6)	125 (3.9)	232 (4.0)	10196 (6.0)
Utah	5 (0.7)	7 (0.2)	10 (0.3)	3 (0.1)	3060 (1.8)
Atlanta	86 (12.3)	40 (1.1)	6 (0.2)	9 (0.2)	5880 (3.5)
Greater Georgia	40 (5.7)	8 (0.2)	7 (0.2)	15 (0.3)	12794 (7.5)
Rural Georgia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	311 (0.2)
Kentucky	4 (0.6)	2 (0.1)	3 (0.1)	4 (0.1)	5748 (3.4)
Louisiana	8 (1.2)	4 (0.1)	0 (0.0)	10 (0.2)	5152 (3.0)

Table 3-1 (continued)

New Jersey	292 (41.8)	198 (5.5)	26 (0.8)	319 (5.5)	18365 (10.8)
Stage at diagnosis					
I	262 (37.5)	1716 (47.3)	1745 (55.0)	2435 (42.0)	74616 (43.8)
II	273 (39.1)	1417 (39.0)	1105 (34.8)	2379 (41.1)	63530 (37.3)
III	110 (15.8)	370 (10.2)	209 (6.6)	673 (11.6)	19612 (11.5)
IV	53 (7.6)	128 (3.5)	113 (3.6)	305 (5.3)	12495 (7.3)
Grade					
I	72 (10.3)	601 (16.6)	790 (24.9)	796 (13.7)	31483 (18.5)
II	222 (31.8)	1421 (39.1)	1377 (43.4)	2277 (39.3)	64271 (37.8)
III	338 (48.4)	1273 (35.1)	833 (26.3)	2216 (38.3)	57063 (33.5)
IV	15 (2.2)	77 (2.1)	38 (1.2)	105 (1.8)	2676 (1.6)
Unknown	51 (7.3)	259 (7.1)	134 (4.2)	398 (6.9)	14760 (8.7)
ER Status					
Positive/borderline	464 (66.5)	2565 (70.6)	2445 (77.1)	4076 (70.4)	119453 (70.2)
Negative	171 (24.5)	705 (19.4)	506 (16.0)	1199 (20.7)	32697 (19.2)
Unknown	63 (9.0)	361 (9.9)	221 (7.0)	517 (8.9)	18103 (10.6)
PR Status					
Positive/borderline	398 (57.0)	2169 (59.7)	2113 (66.6)	3320 (57.3)	98925 (58.1)
Negative	233 (33.4)	1049 (28.9)	769 (24.2)	1769 (30.5)	50024 (29.4)
Unknown	67 (9.6)	413 (11.4)	290 (9.1)	703 (12.1)	21304 (12.5)
Place of birth					
Foreign-born	611 (87.5)	3051 (84.0)	959 (30.2)	5328 (92.0)	28041 (16.5)
U.S.-born	87 (12.5)	580 (16.0)	2213 (69.8)	464 (8.0)	142212 (83.5)

Table 3-2: Risk of late stage breast cancer diagnosis by race, 1999-2009 (n=183,546)

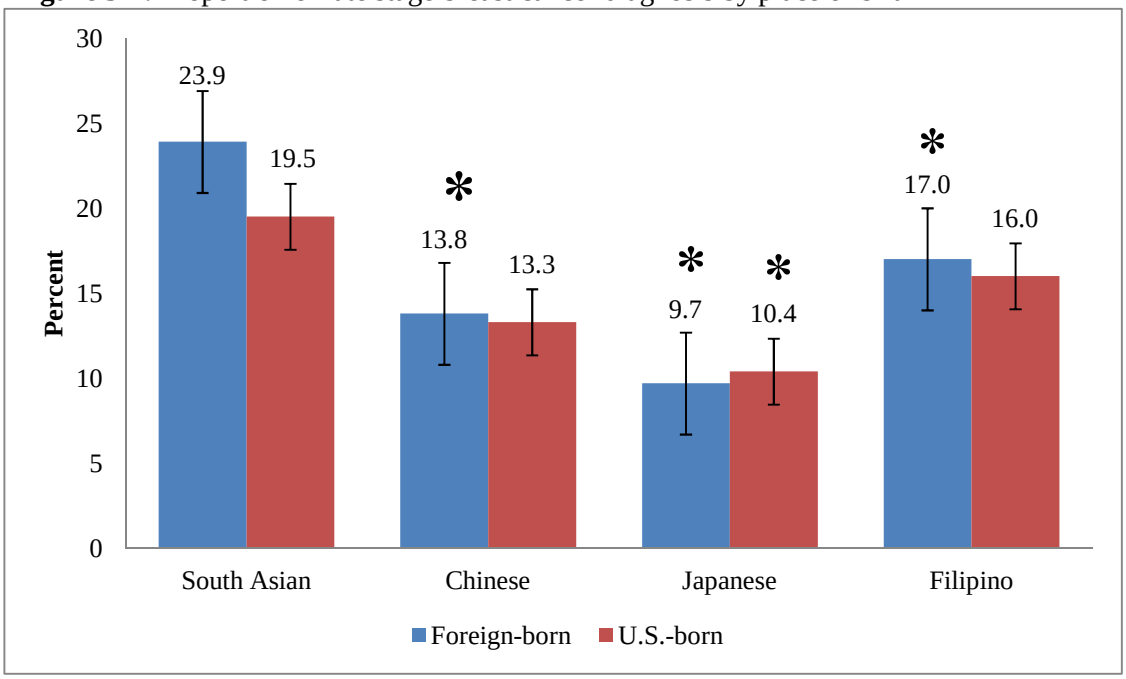
Race	**Age-adjusted model (Race and age only)** OR (95% CI)	***Fully adjusted model** OR (95% CI)
White	1.00 (Referent)	1.00 (Referent)
South Asian	1.24 (1.04, 1.48)	1.07 (0.89, 1.28)
Chinese	0.66 (0.60, 0.73)	0.76 (0.69, 0.83)
Japanese	0.49 (0.44, 0.55)	0.63 (0.55, 0.71)
Filipino	0.86 (0.80, 0.92)	0.98 (0.92, 1.06)
Race	**Age-adjusted model (Race, age, and place of birth only)** OR (95% CI)	****Fully adjusted model** OR (95% CI)
White	1.00 (Referent)	1.00 (Referent)
South Asian	1.18 (0.99, 1.41)	0.97 (0.81, 1.16)
Chinese	0.63 (0.57, 0.70)	0.70 (0.63, 0.77)
Japanese	0.48 (0.43, 0.54)	0.61 (0.54, 0.69)
Filipino	0.82 (0.76, 0.88)	0.89 (0.83, 0.96)
Place of birth		
Foreign	1.00 (Referent)	1.00 (Referent)
U.S.-born	0.93 (0.90, 0.96)	0.87 (0.84, 0.90)

OR indicates odds ratio; 95% CI, confidence interval

*Adjusted for age at diagnosis, year of diagnosis, SEER registry

**Adjusted for age at diagnosis, year of diagnosis, SEER registry, and place of birth

Figure 3-1: Proportion of late stage breast cancer diagnosis by place of birth



✻ Compared with South Asians, proportions significantly different as tested by Chi-square p-value < 0.05

Figure 3-2: Unadjusted Kaplan-Meier curves of overall breast cancer survival comparing South Asians to other Asian subpopulations and non-Hispanic whites

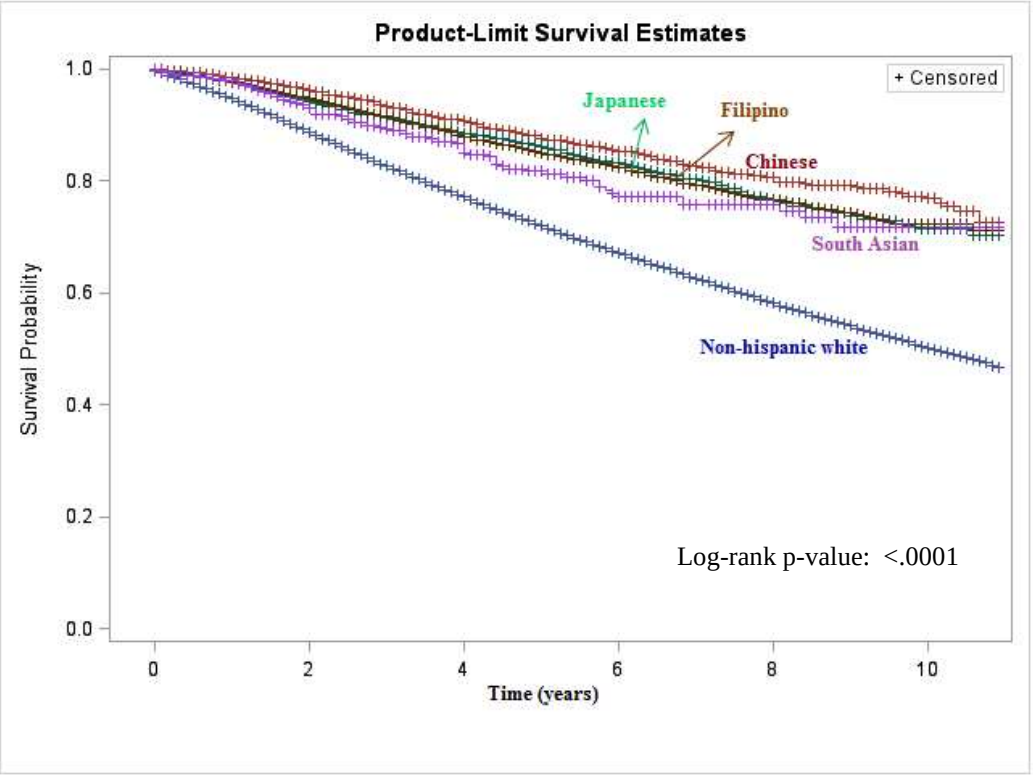


Figure 3-3: Unadjusted Kaplan-Meier curves of overall breast cancer survival comparing South Asians to other Asian subpopulations

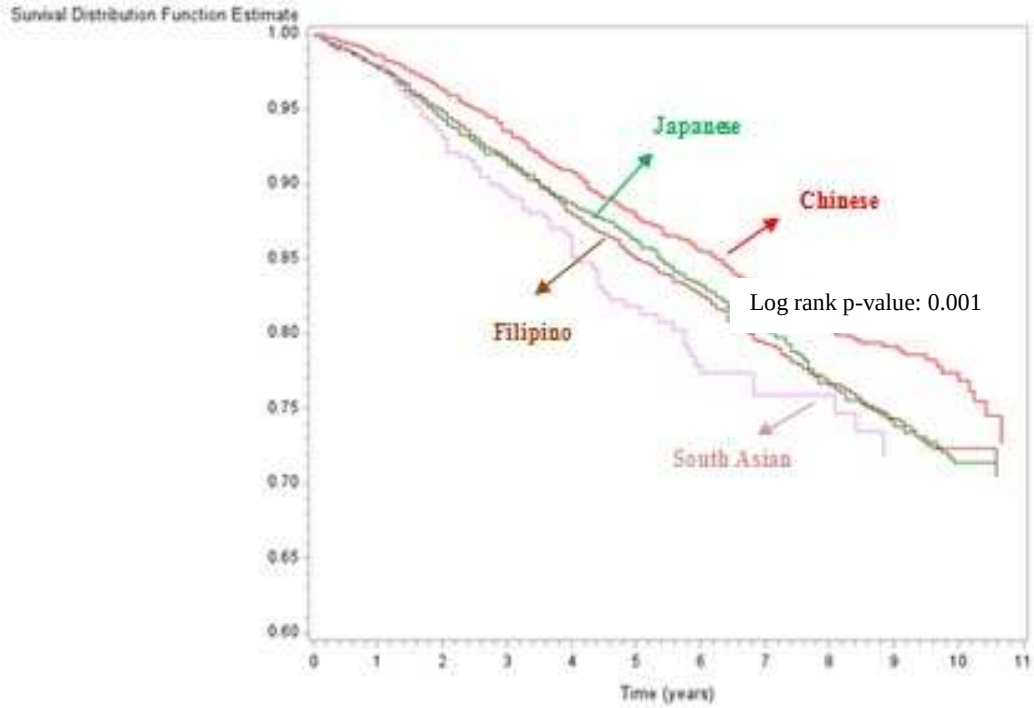
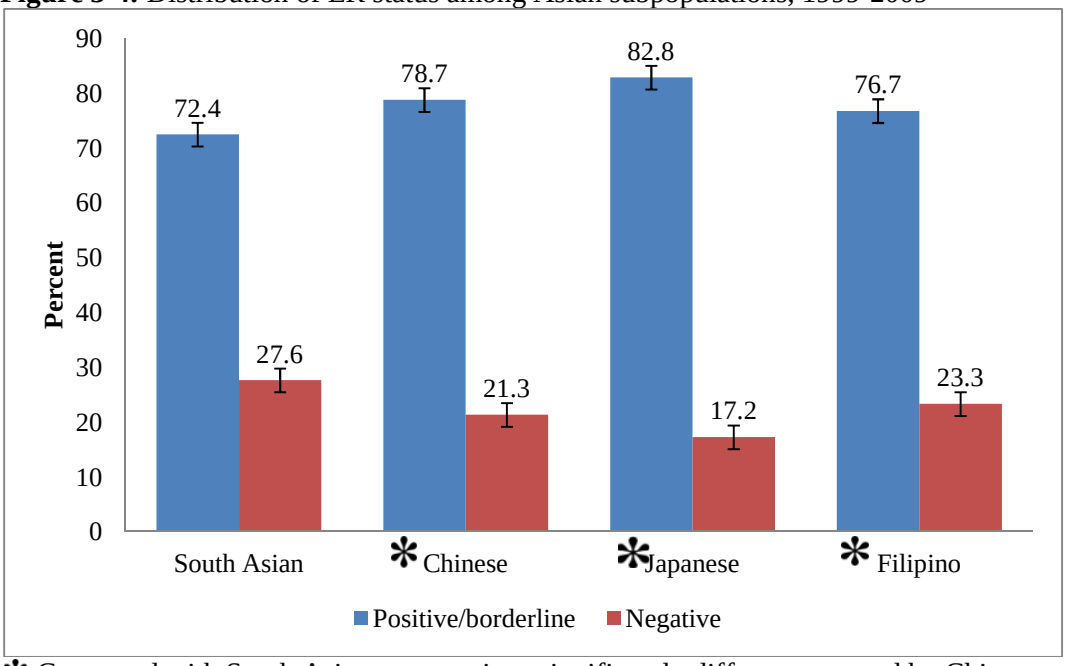
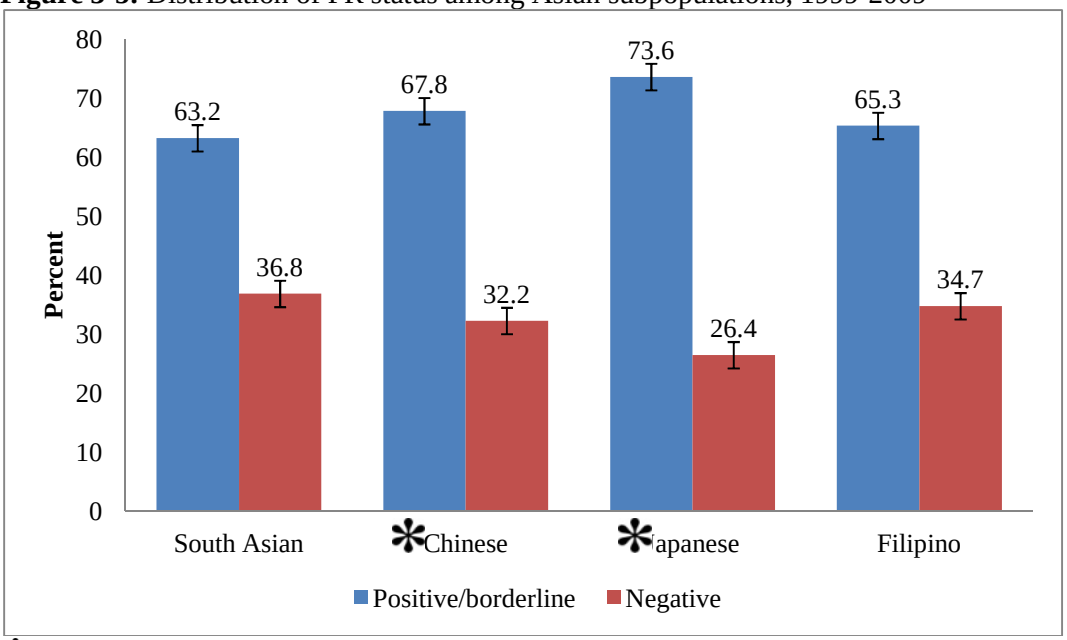


Figure 3-4: Distribution of ER status among Asian subpopulations, 1999-2009



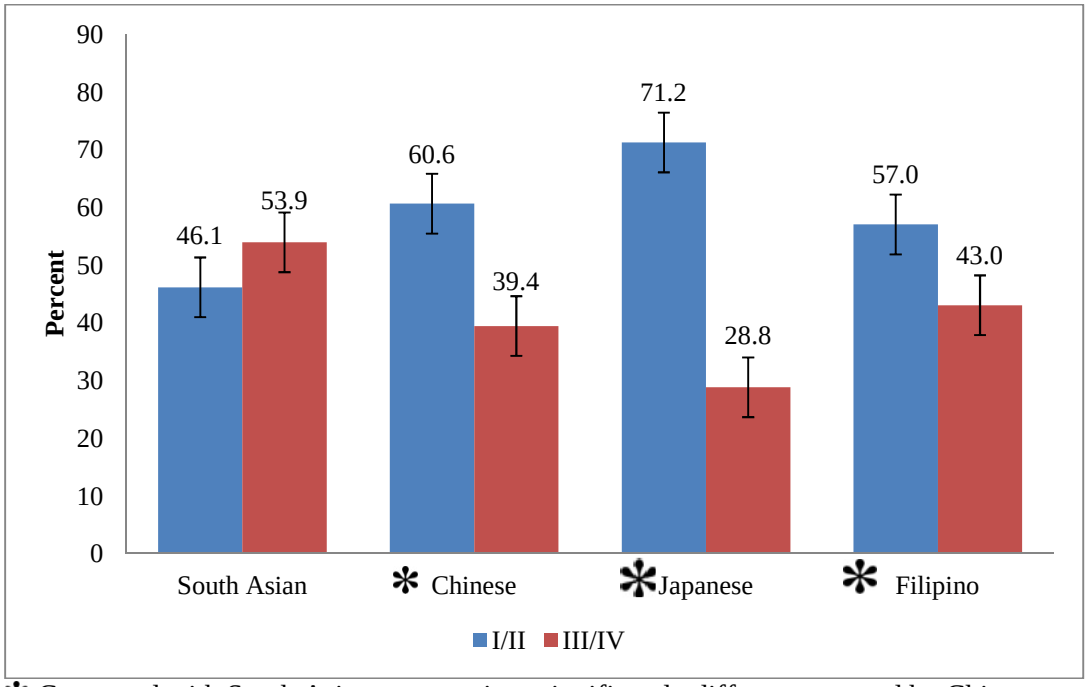
✻ Compared with South Asians, proportions significantly different as tested by Chi-square p-value < 0.05

Figure 3-5: Distribution of PR status among Asian subpopulations, 1999-2009



✻ Compared with South Asians, proportions significantly different as tested by Chi-square p-value < 0.05

Figure 3-6: Distribution of breast tumor grade at diagnosis among Asian subpopulations, 1999-2009



* Compared with South Asians, proportions significantly different as tested by Chi-square p-value < 0.05

Table 3-3: Breast cancer **s**tage-specific survival by race, 1999-2009 (n=150,241)

Race	Age-adjusted model (Race and age only) HR (95% CI)	*Adjusted model HR (95% CI)
Early stage (I/II)		
White	1.00 (Referent)	1.00 (Referent)
South Asian	0.61 (0.44, 0.84)	0.53 (0.38, 0.73)
Chinese	0.47 (0.41, 0.53)	0.70 (0.61, 0.79)
Japanese	0.46 (0.41, 0.51)	0.74 (0.65, 0.84)
Filipino	0.57 (0.52, 0.63)	0.81 (0.73, 0.90)
Late stage (III/IV)		
White	1.00 (Referent)	1.00 (Referent)
South Asian	0.86 (0.63, 1.16)	0.70 (0.51, 0.94)
Chinese	0.56 (0.47, 0.68)	0.72 (0.60, 0.87)
Japanese	0.68 (0.56, 0.83)	0.79 (0.64, 0.98)
Filipino	0.69 (0.61, 0.78)	0.87 (0.77, 0.99)

Race	Age-adjusted model (Race, age and place of birth only) HR (95% CI)	**Adjusted model HR (95% CI)
Early stage (I/II)		
White	1.00 (Referent)	1.00 (Referent)
South Asian	0.79 (0.57, 1.09)	0.61 (0.44, 0.84)
Chinese	0.58 (0.51, 0.66)	0.78 (0.68, 0.89)
Japanese	0.47 (0.42, 0.52)	0.76 (0.67, 0.86)
Filipino	0.74 (0.67, 0.82)	0.93 (0.83, 1.03)
Place of birth		
Foreign	1.00 (Referent)	1.00 (Referent)
U.S. born	1.42 (1.37, 1.48)	1.20 (1.15, 1.25)
Late stage (III/IV)		
White	1.00 (Referent)	1.00 (Referent)
South Asian	1.14 (0.84, 1.54)	0.80 (0.59, 1.09)
Chinese	0.72 (0.60, 0.88)	0.81 (0.66, 0.98)
Japanese	0.71 (0.58, 0.86)	0.81 (0.65, 1.01)
Filipino	0.92 (0.81, 1.04)	0.99 (0.87, 1.13)
Place of birth		
Foreign	1.00 (Referent)	1.00 (Referent)
U.S. born	1.47 (1.40, 1.55)	1.20 (1.13, 1.27)

HR indicates hazard ratio; 95% CI, confidence interval

*Adjusted for age at diagnosis, SEER registry, grade, ER status, PR status

**Adjusted for age at diagnosis, SEER registry, grade, ER status, PR status, and place of birth

Figure 3-7: Association between race/ethnicity and advanced stage at breast cancer diagnosis

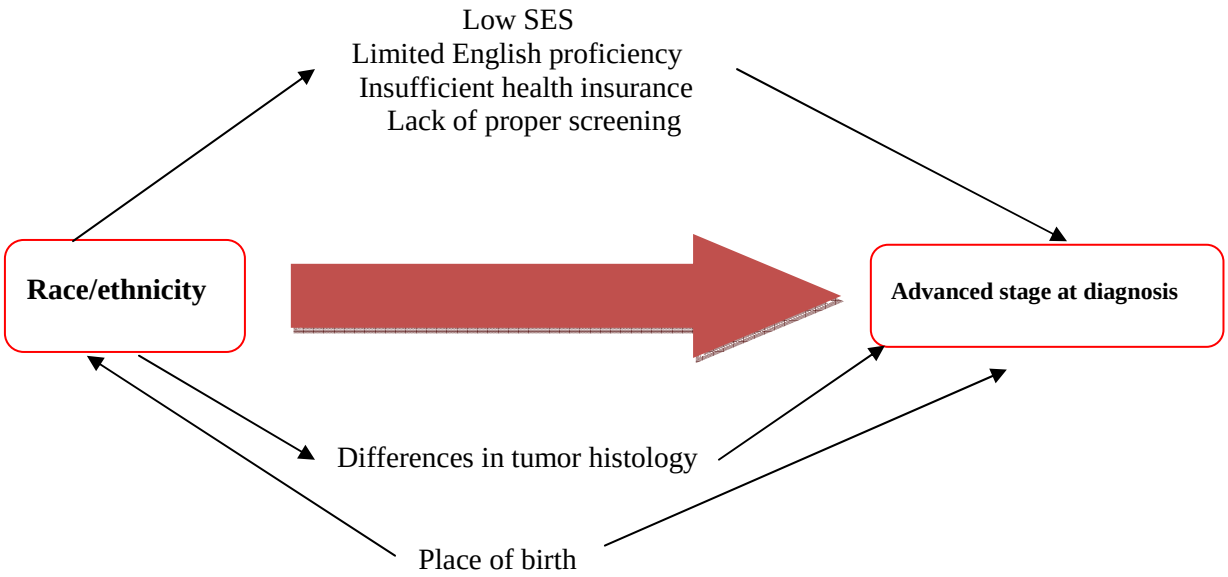
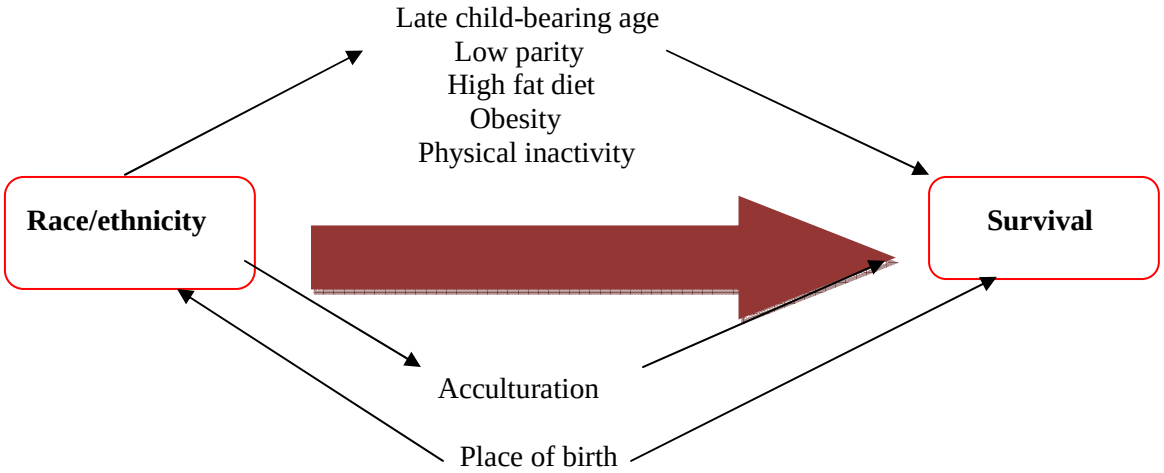


Figure 3-8: Association between race/ethnicity and survival after breast cancer diagnosis



4. PRIMARY CARE AND BREAST CANCER OUTCOMES AMONG ASIAN SUBPOPULATIONS ENROLLED IN MEDICARE

4.1. Abstract

Regular visits with primary care physicians (PCP) significantly impact breast cancer prognosis through increasing the likelihood of early detection. Few studies have utilized population-based data to quantify the association between health care service use and breast cancer outcomes among Asian Americans. We aimed to examine this association among Asians compared to non-Hispanic whites through use of the linked SEER-Medicare database. Racial/ethnic differences in the association between primary care utilization and stage at breast cancer diagnosis was examined using logistic regression. Stage-specific survival following breast cancer diagnosis was examined using Cox regression. Significant associations were found between PCP visits and use of mammography among both Asians and non-Hispanic whites. Asians in the highest quartile of total PCP visits had 57% (OR=0.43; 95% CI 0.27, 0.70) decreased risk of late stage diagnosis compared to those in the lowest quartile. Foreign-born status was significantly protective among Asians diagnosed at late stages, with these cases having 62% (HR=0.38; 95% CI 0.21, 0.70) decreased risk of death compared to those that were U.S.-born. This study provided notable findings regarding health-related behaviors and existing health conditions among older Asian American women which impact breast cancer outcomes. Public health programs which promote regular visits to PCPs must be promoted in this population.

4.2. Background

Breast cancer remains a disease of significant public health concern in the U.S. today. In 2014, it is estimated that approximately 232,670 women will be newly diagnosed with the disease and about 40,000 deaths will occur as a result of breast cancer. Since primary prevention of breast cancer is not a viable option, early detection remains the focus of public health efforts to combat the disease. Prognosis is significantly improved when the disease is detected in its early stages compared to diagnosis at more advanced stages [1].

Physicians involved in primary care can have a significant impact on early detection of breast cancer [2]. They are often the most direct source of information regarding the benefits of cancer prevention methods [3]. It has consistently been reported that a recommendation from a primary care physician (PCP) is strongly associated with receiving mammography screening [4]. In addition, they may also influence breast cancer survival through decreasing diagnostic delays following screenings [5]. Older women in particular have been found to have less knowledge compared to younger women regarding factors related to breast cancer prognosis and treatment and require this information to be provided by their PCPs [6].

Racial/ethnic disparities in receipt of medical services such as screening, diagnosis, and treatment associated with health conditions including cancer have been found to exist in the U.S. As a result, unfavorable disease outcomes are often found among minority populations. Asian/Pacific Islander women in the U.S. report the lowest early detection rates for breast cancer among all other racial/ethnic groups [7]. Despite strong evidence for the association between screening and breast cancer survival and strong

recommendations for mammograms to be conducted regularly, immigrant women are less likely to report having a mammogram in the past two years. Barriers to receipt of mammograms among these groups include lack of primary care and health insurance [8]. A study examining the relationship between Asian Americans and their PCPs reported an association between physician recommendations and cancer screenings in this group. It was also found that among Chinese Americans, the only significant predictor for receiving a mammography was recommendation from a physician [3]. Thus, physician-patient interactions are an integral part of early detection strategy for the Asian American population.

Despite being the fastest- growing minority group in the U.S. today, Asian Americans are a population for which data regarding cancer control and prevention are limited, particularly for immigrants. The majority of studies focusing on cancer prevention strategies in this group have focused on differences in health behaviors and attitudes regarding breast cancer. Few studies have utilized population-based data to quantify the association between health care service use and breast cancer outcomes. Thus, we aim to examine this association among Asians compared to non-Hispanic whites through use of the linked SEER-Medicare database which allows for examination of health care utilization through use of claims data. Roetzheim et al [2] examined this association using cases of all racial/ethnic categories diagnosed between 1994 and 2005. We aim to extend these results to Asian subpopulations in the U.S. by only including this group in addition to non-Hispanic whites. In addition, since Asians in the U.S. are primarily

foreign-born, we will also examine the association between place of birth with the outcomes.

4.3. Methods

The SEER-Medicare database links two large population-based datasets that contain detailed information regarding Medicare beneficiaries diagnosed with cancer. This combined database contains tumor characteristics and demographic information obtained from SEER, in addition to Medicare billing claims for covered health care services received during the time of Medicare eligibility until death. The linkage is updated biennially and about 93% of subjects in the SEER registries aged 65 and over are successfully matched to their Medicare claims.

The SEER-Medicare linked database was used to examine the use of primary care and its association with stage at diagnosis and stage-specific survival among female Medicare beneficiaries diagnosed with primary, invasive breast cancer between January 1, 1999 and December 31, 2009. The analysis was limited to those having at least two years of Medicare claims prior to cancer diagnosis. Thus, only subjects aged 67 years or older identified as South Asian, Chinese, Japanese, Filipino, or non-Hispanic white were eligible for inclusion. These specific countries of origin were chosen for analysis since they are currently the largest Asian subpopulations in the U.S. Those identified in SEER as originating from these countries were classified as Asian in our analyses. Patient data were ascertained by SEER from medical records and available information for each diagnosed case included demographics, tumor characteristics at diagnosis, and year of

diagnosis. Claims data from Medicare were used to calculate total number of PCP visits, use of mammography, and the Charlson comorbidity index.

A total of 332,839 women diagnosed with breast cancer during our study period were available for inclusion in our study sample. Those enrolled in a Medicare health maintenance organization (HMO) during the year of breast cancer diagnosis or the year prior to diagnosis were excluded from the sample since claims for such cases were not available (n=60,543). In addition, those without continuous part A and part B Medicare coverage during the year of diagnosis and the year prior to diagnosis were also excluded since these cases also would not have claims available for analysis (n=131,287). We also excluded cases whose primary cancer diagnosis was not breast cancer (n=4692). Women eligible for Medicare coverage due to end-stage renal disease were excluded due to potential confounding by unknown factors associated with this diagnosis (n=262). These exclusions resulted in a sample size of 136,055. Due to the large size of the non-Hispanic white sample, we utilized simple random sampling to select 10% of this racial/ethnic group for analysis. This resulted in the sample size being reduced to 16,650 cases. We also excluded cases less than 67 years (n=1505) and those with in situ or unknown stage at diagnosis (n=3331). Demographic and tumor characteristics of the eligible Asian cases prior to these exclusions are shown in **Appendix D**. A total of 11,814 women were in the final analytic sample.

Our primary exposure of interest was PCP visits prior to breast cancer diagnosis. We utilized Medicare carrier claims (National Claims History, NCH) to identify primary care utilization using the following CPT codes representing routine office visits: 99201-99205

and 99211-99215. We assessed physician claims during the 24 months prior to breast cancer diagnosis. The Charlson comorbidity index [9] was determined for all cases through use of a macro provided by the NCI utilizing inpatient, outpatient, and physician claims. We assessed claims for comorbidities included in the index for conditions diagnosed up to 23 months prior to cancer diagnosis. We also examined place of birth as a variable of interest in our study. Subjects were classified as either "U.S.-born" or "foreign-born" based on data extracted by SEER from patient medical records or death certificates.

Several covariates were considered to be potential confounders in our multivariable analyses. The models used in the logistic regression analysis adjusted for the effects of age at diagnosis, year of diagnosis, SEER registry, census tract median income (quartiles based on entire sample), comorbidity index, and receipt of mammography within 2 years prior to diagnosis. Age is adjusted for as a confounder due to its varying distributions in the racial/ethnic groups examined and due to the association between older age and increased risk of cancer. Year of diagnosis is taken into account since diagnosis and surveillance methods for cancer detection may have varied during the time period of our study. SEER registry is adjusted for to take into account the location from which the cases originated, since access to care and likelihood of diagnosis may vary between locations. Census tract median income is adjusted for to take into account varying socioeconomic characteristics of the regions included in our study. Comorbidities are taken into account since they may be associated with both race/ethnicity and breast cancer outcomes. Use of mammography is adjusted for due to its effect on stage at diagnosis. The models used in the survival analysis also adjusted for the effects of grade,

ER status, and PR status in addition to the covariates used in the logistic regression analysis. These tumor characteristics are taken into account due to their effect on survival. In addition, these characteristics may vary due to genetic differences between the racial/ethnic groups being compared.

Racial/ethnic differences in the association between primary care utilization and stage at breast cancer diagnosis were examined using logistic regression. Due to small sample sizes within the individual Asian subpopulations, these cases were combined to create an aggregate Asian racial/ethnic category. Subjects were categorized as having early (I or II) or late (III or IV) stage disease using AJCC staging, with the outcome of interest defined as late stage at diagnosis. The exposure of interest, total number of PCP visits, was categorized into quartiles. Logistic regression was conducted to obtain odds ratios and 95% confidence intervals to examine racial/ethnic differences in the association between primary care utilization and late stage at diagnosis while controlling for potential confounding by age at diagnosis, year of diagnosis, SEER registry, census tract median income, comorbidity index, and use of mammography. Age-adjusted associations were first obtained using models with only PCP visits and age as predictors. Fully adjusted associations were then examined which controlled for potential confounders. We also examined the effect of place of birth by including it as a predictor along with PCP visits and the other covariates.

Stage-specific survival following breast cancer diagnosis was also examined among the racial groups of interest. Survival time was provided as a variable in SEER and was calculated by using the date of diagnosis and the earliest of the following: date of death,

date last known to be alive, or the follow-up cutoff date of December 31, 2009. In addition, vital status was provided in the data as either "alive" or "dead." Cox proportional hazards regression was utilized for multivariable adjustment to assess the effects of age, SEER registry, census tract median income, comorbidity index, use of mammography, stage, grade, estrogen receptor (ER) status, and progesterone receptor (PR) status on the observed racial differences in survival. The proportional hazards (PH) assumption was assessed for these covariates prior to inclusion in the models through use of log-log plots and goodness-of-fit tests. Hazard ratios and 95% confidence intervals were obtained to examine the association between PCP visits and stage-specific survival. Age-adjusted associations were obtained using models with only PCP visits and age as predictors. Adjusted estimates were then examined which controlled for potential confounders. We also examined the effect of place of birth by including it as a predictor along with PCP visits and the other covariates. All analyses were conducted using SAS, version 9.3 (SAS Institute, Inc., Cary, NC).

4.4. Results

Table 4-1 shows the distributions of demographic and tumor characteristics for the analytic sample. The Asian cases had a greater proportion of younger women compared to non-Hispanic whites, with 50.3% of subjects diagnosed between the ages of 67 and 75 years. Asians also had more cases in the highest quartile of census tract median income (33%). A slightly higher proportion of Asian cases had a comorbidity score of 1 or greater. Some select characteristics are examined by Asian subpopulation in **Table 4-2**. South Asians had a much greater proportion of cases (63.2%) diagnosed between the ages

of 67 and 75 years compared to the other groups. This group also had the lowest proportion of cases (7.9%) in the lowest quartile of census tract median income and the lowest proportion (13.2%) in the highest quartile of percent with less than high school education. The lowest proportion of cases (63.2%) receiving a mammogram was also found among South Asians.

We assessed the statistical significance of associations between place of birth and other covariates which are likely to have effects on our outcomes of interest. **Table 4-3** shows analysis of the association between place of birth and mammography use among our study subjects. As can be seen in the table, significant associations were detected between place of birth and use of mammography among the two racial/ethnic groups examined. The proportion of cases receiving mammography was lower among the foreign born cases in both populations. We also used an age-adjusted logistic regression model to examine whether the odds of having had a mammography differed between whites and Asians. The odds ratio obtained for this association was non-significant (OR=0.95; 95% CI 0.86, 1.04).

The results of the association between place of birth and comorbidity score are shown in **Table 4-4**. Higher proportions of cases with scores of 1 or greater were found among the foreign-born when examining both Asians only and whites only. **Table 4-5** shows analysis of the association between place of birth and PCP visits. A significant association was not found for these two covariates among the Asian cases. We also examined the association between PCP visits and use of mammography as shown in **Table 4-6**. The majority of cases who did not receive mammograms were in the lowest

quartile of total PCP visits among both Asians and whites. Similarly, the highest proportion of cases receiving mammography was in the highest quartiles of PCP visits.

Table 4-7 shows the results from the multiple logistic regression analysis examining the risk of late stage breast cancer diagnosis associated with total number of PCP visits among Asians and non-Hispanic whites. A significant decreased risk of late stage diagnosis was found among Asians with 20 or more visits compared to those with 0-6 visits. A significant decrease in the risk of late stage diagnosis with increasing number of visits was also found among non-Hispanic whites. In addition, there was a significant 39% increased risk found among foreign-born non-Hispanic whites.

Table 4-8 shows the results of the stage-specific survival analysis. A significant decreased risk of death was found among Asians diagnosed at early stages with 7-12 visits in the fully adjusted model. In addition to significant decreased risk with increasing visits among Whites diagnosed at early stages, a protective association was also found among the foreign-born cases in this group. Foreign-born status was found to be significantly protective among Asians diagnosed at late stages, with these cases having 62% decreased risk of death compared to those that were U.S.-born. Significantly protective associations were again found for White cases diagnosed at late stages.

4.5. Discussion

This study found significant effects of place of birth when examining the association between health-related behaviors, such as PCP visits and use of screening

mammography, and breast cancer outcomes. Utilization of primary care services was found to be associated with decreased risk of late stage diagnosis as well as decreased risk of death among Asians and non-Hispanic whites examined in our analyses.

Due to limited sample sizes in the Asian cases, our subpopulations of interest were combined to create one aggregate racial/ethnic group in our analyses. However, a detailed examination of these individual subpopulations revealed notable demographic differences that likely play a role in breast cancer outcomes among these groups. Asians as a whole were found to be diagnosed at younger ages compared to non-Hispanic whites. A closer assessment of the individual subpopulations revealed that South Asians had the highest proportion of cases between the ages of 67 and 75 years. This is consistent with previous findings reporting younger cases in this group compared to non-Hispanic whites [10]. In addition, our findings are consistent with previous studies which have found this particular Asian subpopulation to be of high socioeconomic status. The majority of South Asian cases in our analyses resided in areas of higher median income and educational attainment compared to the other Asian groups. Though South Asians in the U.S. are generally of higher socioeconomic status compared to other minority populations, they have consistently been found to under-utilize screening services, such as mammography [11]. This was confirmed by our results which showed that this group had the lowest proportion of cases (63.2%) receiving mammography. Though breast cancer incidence has previously been examined among South Asians reported in SEER registries, our study is the first to our knowledge examining these characteristics in Medicare beneficiaries belonging to this group.

Place of birth is a covariate which has not been examined extensively in studies of cancer among Asians in the U.S. We examined the association between place of birth and several covariates in our study which likely have effects on our outcomes of interest. Significant associations were found between place of birth and use of mammography. In particular, the proportion of cases who received mammography was lower among the foreign born compared to U.S.-born cases in both populations. It has previously been found that the Asian population in the U.S. is primarily composed of immigrants, with the majority of them reporting foreign birth [12]. Thus, they are more likely to have cultural beliefs regarding health that may potentially have an adverse impact on outcomes related to cancer. These beliefs, such as self-sufficiency and greater emphasis on familial obligations rather than individual health, likely contribute to the lack of preventive care sought by this minority group [13]. Significant associations were also found between place of birth and comorbidity scores. Higher proportions of cases with scores of 1 or greater were found among the foreign-born when examining both Asians only and whites only. Diabetes is one comorbid condition that is highly prevalent among Asian groups. Asian Americans are at greater risk for diabetes compared to non-Hispanic whites. Japanese Americans in particular have been found to be twice as likely to develop diabetes compared to non-Hispanic whites [14]. A study conducted among Indian immigrants in Georgia reported that the overall prevalence of diabetes among Indians was 18.3%, a rate which was higher compared to Whites, Blacks, and Hispanics [15]. The association between place of birth and PCP visits was not statistically significant. However, the highest proportion of foreign-born Asian cases was found to be in the lowest quartile of total PCP visits. A previous study examining the breast cancer

experience of Asian American women found that they are not actively engaged in matters related to their own health. This is especially common among recent immigrants who are less acculturated to western culture. In addition, these women have been reported to depend on both westernized as well as alternative remedies for ailments [7]. Most importantly, significant associations were detected between PCP visits and use of mammography among both Asians and non-Hispanic whites. Previous studies have reported that physicians serve as significant liaisons regarding public health issues among Asian Americans. They are the most essential source of knowledge regarding cancer risk and serve as primary resources for providing screening information and recommendations [3]. A study examining preventive health services delivery to South Asians in the U.S. found that the likelihood of being current with preventive health care services was greater when one had a regular source of healthcare [16]. Thus, this association is of public health importance when creating interventions targeted towards improving breast cancer outcomes in these groups.

Our findings provided further evidence for favorable breast cancer outcomes associated with regular PCP visits. Primary care visits were associated with decreased risk of late stage diagnosis of breast cancer among both Asians and non-Hispanic whites. Asians in the highest quartile of total PCP visits had 57% (OR=0.43; 95% CI 0.27, 0.70) decreased risk of late stage diagnosis compared to those in the lowest quartile. This significant association remained after controlling for potential confounders. Both foreign-born Asians and non-Hispanic whites were found to have increased risk for late stage at diagnosis. Regular visits with a PCP likely affect breast cancer stage at diagnosis by increasing the likelihood of earlier diagnosis following onset of symptoms or by reducing

diagnostic delays following abnormal mammogram results. In addition, regular visits may be associated with overall healthier lifestyles that are related to progression of disease [2].

Increasing visits was associated with decreased risk of death in our survival analysis. Due to limited sample sizes, the majority of effect estimates did not reach statistical significance for the Asian cases. Foreign-born status was significantly protective among Asians diagnosed at late stages, with these cases having 62% (HR=0.38; 95% CI 0.21, 0.70) decreased risk of death compared to those that were U.S.-born. Place of birth may be used as a measure of acculturation to support this finding. Breast cancer cases that are U.S.-born likely have an increased risk of death because they practice Westernized lifestyles, such as diets high in fat intake, that are known to increase breast cancer risk. It has been well established that risk factors associated with Westernized culture such as obesity, physical inactivity, diets high in fat, late child bearing age, and low parity, are associated with decreased survival following breast cancer diagnosis [17].

Comorbidities associated with breast cancer are a factor which has not been examined extensively among Asian immigrants in the U.S. When examining the individual Asian subpopulations used in our analyses, South Asians and Filipinos had nearly half of all cases with comorbidity scores of 1 or greater. It has previously been suggested that racial/ethnic differences in the presence of comorbidities may also lead to disparities in the use of screening methods, such as mammography [18]. This is likely due to competing demand that those with chronic conditions must face when determining allotment of time,

resources, and attention. This competing risk will undoubtedly take away from the delivery of preventive health services [19]. The relatively high prevalence of comorbidities among Asian subpopulations must be taken into consideration when examining breast cancer outcomes among these cases.

When considering the Asian SEER cases aged 67 years and older and belonging to our subpopulations of interest diagnosed during our study period, we found that the percentage of these cases also found in SEER-Medicare ranged from 50-75%. The percentage of cases in SEER also found in SEER-Medicare was as follows: 70.3% of Chinese cases, 74.9% of Japanese cases, 49.8% of Filipino cases, and 75.2% of South Asian cases. Inclusion in the SEER-Medicare database is likely dependent on factors such as recency of immigration to the U.S. and socioeconomic status.

To our knowledge, this is the first study to examine Asian subpopulations using the linked SEER-Medicare database. In addition, previous studies examining breast cancer outcomes in the Asian population in the U.S. have not taken comorbidities into account. We were also able to provide further support for the significant effect of place of birth on cancer outcomes. Studies examining the effect of primary care utilization in this group are also limited. Our findings revealed strong associations between PCP visits and stage at diagnosis and stage-specific survival. This is an association that needs to be studied further among the individual subpopulations that comprise the Asian immigrant population in the U.S.

A few limitations regarding the use of claims data must be taken into account when interpreting the findings of our study. Our analysis utilized data from Medicare, a federal fee-for-service insurance provider. Thus, since all of the subjects included in our analyses were insured under this program, our findings may not apply to those not covered by Medicare. It is also important to note that in order to receive Medicare coverage among those over 65 years of age, it is required that one must have been employed in the U.S. for a minimum of 10 years. Thus, those not covered by Medicare are likely recent immigrants and may have differing socioeconomic status compared to those covered by Medicare. In addition, the analysis is subject to limitations associated with claims data, such as incomplete data and coding errors. We also did not have information on the specific reason for a patient's PCP visit. The data provided by SEER-Medicare did not allow for examination of individual Asian subpopulations since our cases were limited to Medicare beneficiaries living in areas covered by SEER registries.

Conclusion

Our study provided notable findings regarding health-related behaviors and existing health conditions among older Asian American women which impact breast cancer outcomes. Though statistical significance was not achievable for the individual subpopulations in our multivariable analyses, notable differences were found when comparing Asian Americans as an aggregate to non-Hispanic whites. The proportion of cases receiving mammography was lower among the foreign born compared to U.S.-born cases. Significant associations were also detected between PCP visits and use of mammography. Thus, programs which promote regular visits to PCPs must be promoted

in this population. The SEER-Medicare population in general is unique since these subjects have medical insurance and have equal access to healthcare. However, utilization of these services differ by race/ethnicity since variations in the breast cancer outcomes examined were observed. Reasons for these differences in outcomes in this population need to be examined further in future studies. Future public health interventions which target these Asian immigrants also need to account for factors such as place of birth and recency of immigration in order to meet the needs of this rapidly growing minority population in the U.S.

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4.7. Tables and Figures

Table 4-1: Demographic and tumor characteristics among 11, 814 female Medicare beneficiaries diagnosed with invasive breast cancer in SEER-Medicare

Characteristic	Asian (n=2325)	Non-hispanic white (n=9489)	*P-value
Age at diagnosis, y			
67-70	416 (17.9)	1565 (16.5)	<.0001
71-75	753 (32.4)	2415 (25.5)	
76-80	590 (25.4)	2422 (25.5)	
81-85	372 (16.0)	1804 (19.0)	
86+	194 (8.3)	1283 (13.5)	
Year of diagnosis			
1999-2001	514 (22.1)	2437 (25.7)	<.0001
2002-2004	633 (27.2)	2759 (29.1)	
2005-2007	720 (31.0)	2536 (26.7)	
2008-2009	458 (19.7)	1757 (18.5)	
Income (of census tract)			
Quartile 1	420 (18.1)	2534 (26.7)	<.0001
Quartile 2	500 (21.5)	2454 (25.9)	
Quartile 3	628 (27.0)	2325 (24.5)	
Quartile 4	766 (33.0)	2116 (22.3)	
Unknown	11 (0.5)	60 (0.6)	
Education (% <HS in census tract)			
Quartile 1	613 (26.4)	2743 (28.9)	0.007
Quartile 2	538 (23.1)	2341 (24.7)	
Quartile 3	555 (23.9)	2101 (22.1)	
Quartile 4	608 (26.2)	2244 (23.7)	
Unknown	11 (0.5)	60 (0.6)	
Total primary care visits, n			
0-6	637 (27.4)	2660 (28.0)	0.419
7-12	563 (24.2)	2383 (25.1)	
12-20	577 (24.8)	2206 (23.3)	
20+	548 (23.6)	2240 (23.6)	
Comorbidity score			
0	1457 (62.7)	6112 (64.4)	0.009
1	578 (24.9)	2087 (22.0)	
2+	290 (12.5)	1290 (13.6)	

Table 4-1 (continued)

Mammography			
No	710 (30.5)	2921 (30.8)	0.818
Yes	1615 (69.5)	6568 (69.2)	
Place of birth			
U.S.-born	627 (27.0)	4408 (46.5)	<.0001
Foreign-born	918 (39.5)	479 (5.1)	
Unknown	780 (33.6)	4602 (48.5)	
Stage at diagnosis			
Early	2082 (89.6)	8351 (88.0)	0.038
Late	243 (10.5)	1138 (12.0)	
Grade at diagnosis			
I	508 (21.9)	2213 (23.3)	0.018
II	1022 (44.0)	3836 (40.4)	
III	506 (21.8)	2218 (23.4)	
IV	26 (1.1)	80 (0.8)	
Unknown	263 (11.3)	1142 (12.0)	
ER Status			
Positive/borderline	1679 (72.2)	6886 (72.6)	0.916
Negative	302 (13.0)	1203 (12.7)	
Unknown	344 (14.8)	1400 (14.8)	
PR Status			
Positive/borderline	1415 (60.9)	5763 (60.7)	0.994
Negative	557 (24.0)	2281 (24.0)	
Unknown	353 (15.2)	1445 (15.2)	

*****P-values based on the χ^2 test

Table 4-2: Demographic and tumor characteristics among 2, 325 Asian female Medicare beneficiaries diagnosed with invasive breast cancer in SEER-Medicare

Characteristic	South Asian (n=76)	Chinese (n=584)	Japanese (n=1040)	Filipino (n=625)	*P-value
Age at diagnosis, y					
67-70	16 (21.1)	97 (16.6)	172 (16.5)	131 (21.0)	<.0001
71-75	32 (42.1)	161 (27.6)	331 (31.8)	229 (36.6)	
76-80	13 (17.1)	150 (25.7)	281 (27.0)	146 (23.4)	
81-85	9 (11.8)	107 (18.3)	171 (16.4)	85 (13.6)	
86+	6 (7.9)	69 (11.8)	85 (8.2)	34 (5.4)	
Income (of census tract)					
Quartile 1	6 (7.9)	123 (21.1)	173 (16.6)	118 (18.9)	<.0001
Quartile 2	11 (14.5)	105 (18.0)	238 (22.9)	146 (23.4)	
Quartile 3	22 (29.0)	137 (23.5)	287 (27.6)	182 (29.1)	
Quartile 4	37 (48.7)	213 (36.5)	341 (32.8)	175 (28.0)	
Unknown	0 (0.0)	6 (1.0)	1 (0.1)	4 (0.6)	
Education (% <HS in census tract)					
Quartile 1	28 (36.8)	183 (31.3)	299 (28.8)	103 (16.5)	<.0001
Quartile 2	19 (25.0)	115 (19.7)	270 (26.0)	134 (21.4)	
Quartile 3	19 (25.0)	114 (19.5)	258 (24.8)	164 (26.2)	
Quartile 4	10 (13.2)	166 (28.4)	212 (20.4)	220 (35.2)	
Unknown	0 (0.0)	6 (1.0)	1 (0.1)	4 (0.6)	
Total primary care visits, n					
0-6	19 (25.0)	155 (26.5)	259 (24.9)	204 (32.6)	<.0001
7-12	24 (31.6)	114 (19.5)	278 (26.7)	147 (23.5)	
12-20	17 (22.4)	139 (23.8)	276 (26.5)	145 (23.2)	
20+	16 (21.1)	176 (30.1)	227 (21.8)	129 (20.6)	
Comorbidity score					
0	42 (55.3)	357 (61.1)	720 (69.2)	338 (54.1)	<.0001
1	24 (31.6)	143 (24.5)	240 (23.1)	171 (27.4)	
2+	10 (13.2)	84 (14.4)	80 (7.7)	116 (18.6)	
Mammography					
No	28 (36.8)	197 (33.7)	267 (25.7)	218 (34.9)	<.0001
Yes	48 (63.2)	387 (66.3)	773 (74.3)	407 (65.1)	

***P-values based on the χ^2 test

Table 4-3: Association between place of birth and use of mammography

	Use of mammography		
All (Whites & Asians)	**No**	**Yes**	***P-value**
U.S.-born	1723 (34.2)	3312 (65.8)	<.0001
Foreign born	502 (35.9)	895 (64.1)	
Unknown	1406 (26.1)	3976 (73.9)	
Asians only			
U.S.-born	168 (26.8)	459 (73.2)	0.0018
Foreign born	318 (34.6)	600 (65.4)	
Unknown	224 (28.7)	556 (71.3)	
Whites only			
U.S.-born	1555 (35.3)	2853 (64.7)	<.0001
Foreign born	184 (38.4)	295 (61.6)	
Unknown	1182 (25.7)	3420 (74.3)	

*P-values based on chi-square test of independence

Table 4-4: Association between place of birth and comorbidity score

	Comorbidity score			
All (Whites & Asians)	**0**	**1**	**2+**	***P-value**
U.S.-born	3102 (61.6)	1175 (23.3)	758 (15.1)	<.0001
Foreign born	829 (59.3)	348 (24.9)	220 (15.8)	
Unknown	3638 (67.6)	1142 (21.2)	602 (11.2)	
Asians only				
U.S.-born	406 (64.8)	156 (24.9)	65 (10.4)	0.088
Foreign born	552 (60.1)	231 (25.2)	135 (14.7)	
Unknown	499 (64.0)	191 (25.0)	90 (11.5)	
Whites only				
U.S.-born	2696 (61.2)	1019 (23.1)	693 (15.7)	<.0001
Foreign born	277 (57.8)	117 (24.4)	85 (17.8)	
Unknown	3139 (68.2)	951 (20.7)	512 (11.1)	

*P-values based on chi-square test of independence

Table 4-5: Association between place of birth and PCP visits

	Physician visits				
All (Whites & Asians)	**0-6**	**7-12**	**13-20**	**20+**	***P-value**
U.S.-born	1456 (28.9)	1226 (24.4)	1144 (22.7)	1209 (24.0)	<.0001
Foreign born	411 (29.4)	305 (21.8)	313 (22.4)	368 (26.3)	
Unknown	1430 (26.6)	1415 (26.3)	1326 (24.6)	1211 (22.5)	
Asians only					
U.S.-born	150 (23.9)	163 (26.0)	162 (25.8)	152 (24.2)	0.152
Foreign born	273 (29.7)	213 (23.2)	209 (22.8)	223 (24.3)	
Unknown	214 (27.4)	187 (24.0)	206 (26.4)	173 (22.2)	
Whites only					
U.S.-born	1306 (29.6)	1063 (24.1)	982 (22.3)	1057 (24.0)	<.0001
Foreign born	138 (28.8)	92 (19.2)	104 (21.7)	145 (30.3)	
Unknown	1216 (26.4)	1228 (26.7)	1120 (24.3)	1038 (22.6)	

*****P-values based on chi-square test of independence

Table 4-6: Association between PCP visits and use of mammography

	Physician visits				
All (Whites & Asians)	**0-6**	**7-12**	**13-20**	**20+**	***P-value**
No	1650 (45.4)	803 (22.1)	620 (17.1)	558 (15.4)	<.0001
Yes	1647 (20.1)	2143 (26.2)	2163 (26.4)	2230 (27.3)	
Asians only					
No	331 (46.6)	138 (19.4)	130 (18.3)	111 (15.6)	<.0001
Yes	306 (19.0)	425 (26.3)	447 (27.7)	437 (27.1)	
Whites only					
No	1319 (45.2)	665 (22.8)	490 (16.8)	447 (15.3)	<.0001
Yes	1341 (20.4)	1718 (26.2)	1716 (26.1)	1793 (27.3)	

*P-values based on chi-square test of independence

Table 4-7: Risk of late stage breast cancer diagnosis by race/ethnicity among Asian subpopulations enrolled in Medicare, 1999-2009 (n=11, 814)

Total number of visits	Age-adjusted model (visits and age only) OR (95% CI)	*Fully adjusted model OR (95% CI)
Asian		
0-6	1.00 (Referent)	1.00 (Referent)
7-12	0.54 (0.38, 0.78)	0.67 (0.44, 1.00)
13-20	0.64 (0.45, 0.91)	0.81 (0.54, 1.22)
20+	0.41 (0.27, 0.60)	0.43 (0.27, 0.70)
Place of birth		
U.S.-born		1.00 (Referent)
Foreign-born		1.19 (0.79, 1.79)
Unknown		0.74 (0.48, 1.12)
White		
0-6	1.00 (Referent)	1.00 (Referent)
7-12	0.55 (0.46, 0.64)	0.66 (0.55, 0.78)
13-20	0.51 (0.43, 0.60)	0.65 (0.53, 0.78)
20+	0.44 (0.37, 0.53)	0.54 (0.44, 0.66)
Place of birth		
U.S.-born		1.00 (Referent)
Foreign-born		1.39 (1.07, 1.80)
Unknown		0.51 (0.44, 0.59)

*Adjusted for age at diagnosis, year of diagnosis, SEER registry, census tract median income, comorbidity score, mammography, place of birth

Table 4-8: Stage-specific breast cancer survival by race/ethnicity among Asian subpopulations enrolled in Medicare, 1999-2009 (n=11, 371)

Total number of visits	Age-adjusted model (visits and age only) HR (95% CI)	*Fully adjusted model HR (95% CI)
Early stage (I/II)		
Asian		
0-6	1.00 (Referent)	1.00 (Referent)
7-12	0.72 (0.54, 0.97)	0.66 (0.49, 0.90)
13-20	0.73 (0.54, 0.97)	0.76 (0.56, 1.04)
20+	1.13 (0.87, 1.48)	1.00 (0.74, 1.35)
Place of birth		
U.S.-born		1.00 (Referent)
Foreign-born		0.80 (0.61, 1.05)
Unknown		0.35 (0.25, 0.49)
White		
0-6	1.00 (Referent)	1.00 (Referent)
7-12	0.80 (0.72, 0.90)	0.78 (0.69, 0.87)
13-20	0.87 (0.78, 0.97)	0.75 (0.67, 0.85)
20+	1.15 (1.04, 1.29)	0.90 (0.80, 1.01)
Place of birth		
U.S.-born		1.00 (Referent)
Foreign-born		0.76 (0.64, 0.91)
Unknown		0.24 (0.21, 0.26)
Late stage (III/IV)		
Asian		
0-6	1.00 (Referent)	1.00 (Referent)
7-12	1.14 (0.63, 2.04)	0.96 (0.49, 1.90)
13-20	0.82 (0.47, 1.45)	0.73 (0.39, 1.37)
20+	1.57 (0.89, 2.76)	1.20 (0.59, 2.45)
Place of birth		
U.S.-born		1.00 (Referent)
Foreign-born		0.38 (0.21, 0.70)
Unknown		0.25 (0.12, 0.53)
White		
0-6	1.00 (Referent)	1.00 (Referent)
7-12	0.76 (0.62, 0.94)	0.78 (0.63, 0.97)
13-20	0.71 (0.57, 0.88)	0.75 (0.59, 0.95)
20+	0.78 (0.63, 0.98)	0.73 (0.57, 0.94)
Place of birth		
U.S.-born		1.00 (Referent)
Foreign-born		0.62 (0.46, 0.84)
Unknown		0.32 (0.25, 0.39)

*Adjusted for age at diagnosis, SEER registry, census tract median income, comorbidity score, mammography, grade at diagnosis, ER status, PR status, place of birth

5. CONCLUSIONS AND RECOMMENDATIONS

There is currently a significant lack of epidemiological studies examining the cancer burden of the South Asian population in the United States today, despite the recent rapid growth of this immigrant group. As this predominant Asian subpopulation in the U.S. continues to increase, it is essential that we understand the cancer burden impacting this group in order to tailor prevention efforts to address the needs of this expanding population. Existing literature has included this group in an aggregate racial/ethnic category known as Asian/Pacific Islander (PI). The racial/ethnic category often referred to as Asian/PI is in fact comprised of several heterogeneous populations with very different cultural and lifestyle characteristics which lead to differences in cancer outcomes. The use of such combined categorizations of race obscures significant differences in cancer occurrence patterns among specific subpopulations, such as those of South Asian origin.

In this study we utilized data from the National Cancer Institute's SEER program and the linked SEER-Medicare database to examine differences in cancer outcomes, specifically stage at diagnosis and stage-specific survival, among South Asians and the three other predominant Asian subpopulations in the U.S. compared to non-Hispanic whites. Three infection-associated cancers which are common among those of Asian origin were examined in addition to breast cancer. While these outcomes have been studied among these groups in California, limited studies have utilized nationwide data when examining outcomes in these groups. In addition, this study greatly contributes to the existing

literature by also examining the independent effect of place of birth when examining these cancer outcomes.

In our study of infection-associated cancers, it was found that South Asians had the highest proportion (48%) of late stage liver cancer cases compared to the other Asian subpopulations examined. The non-significance of the advanced stage at diagnosis odds ratio obtained for South Asians in this analysis was likely due to the small sample size of this group. However, this finding of increased late stage diagnosis is of clinical significance in this Asian subpopulation due to the recent emergence of diabetes as an independent risk factor for liver cancer. India reports the highest prevalence of diabetes compared to other countries in the neighboring region, with rates ranging from 18.6% in urban areas to 9.2% in rural areas [1]. In addition, a study conducted in India reported that diabetic patients with liver cancer had more advanced tumors of larger size and increased likelihood of intraheptic bile duct involvement [2]. These findings highlight the need for improved monitoring among those of South Asian origin who are diabetic or diagnosed with other risk factors associated with liver cancer in order to increase the likelihood of early stage diagnosis.

When examining breast cancer outcomes among the Asian subpopulations, the highest risk for late stage diagnosis when compared to non-Hispanic whites was found among South Asians. Though non-significant, the adjusted model which also accounted for place of birth found 3% (OR=0.97; 95% CI 0.81, 1.16) reduced risk for late stage diagnosis for this group compared to non-Hispanic whites. However, much lower risk was found

among the other Asian groups examined. Diagnosis of breast cancer at an advanced stage of disease greatly increases the risk of death. Studies among immigrant women in the U.S. have found that they are at increased risk for unfavorable breast cancer outcomes due to limited English language proficiency, insufficient health insurance, and barriers to access such as social exclusion. As a result, they are less likely to have sufficient knowledge regarding cancer prevention and consequently less likely to receive adequate screening prior to diagnosis of cancer [3]. However, South Asians have in fact been categorized as the highest educated, highest paid, and best insured immigrants in the U.S. Despite seemingly high socioeconomic status, South Asian origin is reportedly associated with insufficient adherence to breast cancer prevention recommendations, such as regular screenings. This is especially true among recent immigrants to the U.S [4]. The lack of proper prevention methods likely contributes greatly to the advanced stage presentation of breast cancer found among South Asian women.

Our findings further revealed that South Asians had the most favorable stage-specific survival for both early and late stage diagnosis among the other Asian subpopulations when compared to non-Hispanic whites. The adjusted model which also controlled for place of birth showed that among those diagnosed with early-stage disease, South Asians had 39% significant reduced risk (95% CI 0.44, 0.84) of death when compared to non-Hispanic whites. Among those diagnosed with late-stage disease, this group had 20% reduced risk (95% CI 0.59, 1.09) of death when compared to non-Hispanic whites. The recency of immigration to the U.S. for the majority of those that comprise this group is likely an explanation for this finding. The majority of South Asians in the U.S. today are

recent immigrants. Only approximately 9% of Asian Indians and 6% of Pakistanis older than 18 years were born in the U.S. according to the 2000 U.S. census. Most adults that comprise this Asian subpopulation immigrated to the U.S. after 1985. As a result of their recent immigration, the extent of acculturation present in this group is relatively low compared to other immigrant groups in the U.S [5]. Acculturation plays an important role since reproductive and lifestyle characteristics known to decrease breast cancer survival, such as late child-bearing age, obesity, and physical inactivity, are associated with westernized culture.

Through individual examination of the major Asian subpopulations that comprise the aggregate Asian/PI racial/ethnic category in the U.S., our findings revealed heterogeneity in risk of late stage at diagnosis and stage-specific survival of three common infection-associated cancers and breast cancers. Our findings revealed that South Asians were more likely to present with advanced stage at diagnosis for these cancers compared to the other Asian subpopulations we examined. Thus, there is a true need for more individualized prevention for this major immigrant population in the U.S. in order to improve outcomes associated with cancer. In addition, our results provided further evidence for the inappropriate use of an aggregate racial/ethnic category when examining these subpopulations since true differences in outcomes exist.

Due to small sample sizes, we were not able to examine the Asian subpopulations individually in our analyses utilizing the SEER-Medicare database. However, our findings revealed significant effects of place of birth when examining the association

between factors such as use of screening mammography and comorbidities and breast cancer outcomes. Significant associations were found between place of birth and use of mammography. In particular, the proportion of cases receiving mammography was lower among the foreign born compared to U.S.-born cases in both Asians and non-Hispanic whites. Our results also revealed significant associations between place of birth and comorbidity scores. Higher proportions of cases with scores of 1 or greater were found among the foreign-born when examining both Asians only and whites only. In addition, our findings provided further evidence for favorable breast cancer outcomes associated with regular primary care physician visits. Primary care visits were associated with decreased risk of late stage diagnosis of breast cancer among both Asians and non-Hispanic whites. Asians in the highest quartile of total physician visits had 57% (OR=0.43; 95% CI 0.27, 0.70) decreased risk of late stage diagnosis compared to those in the lowest quartile.

Our analysis of Asian subpopulations using SEER-Medicare provided important findings regarding health-related behaviors and existing health conditions among older Asian American women which impact breast cancer outcomes. To our knowledge, this is the first study to examine Asian subpopulations using the linked SEER-Medicare database. The majority of studies focusing on cancer prevention strategies in this group have focused on differences in health behaviors and attitudes regarding breast cancer. Few studies have utilized population-based data to quantify the association between health care services used and breast cancer outcomes among Asian American immigrants.

Recommendations

Cancer registries are the most comprehensive data sources available for assessment of cancer incidence and outcomes. Thus, it is imperative that these data are up-to-date and as complete as possible. One variable that must be improved with regard to completeness is place of birth. This variable was missing for approximately 30% of the Asian subpopulations examined and almost 50% of the non-Hispanic white population. Previous research has provided evidence to support a strong association between environmental exposures and subsequent cancer outcomes. Complete data regarding place of birth may have resulted in stronger, more statistically significant associations between this variable and stage at diagnosis or stage-specific survival. Cancer registries should improve their ascertainment of this important variable when collecting demographic data from patients.

SEER is currently the most complete source for cancer data on Asian subpopulations in the U.S. However, it does not have reporting registries in areas known to have high concentrations of Asian residents. Coverage is not available in areas such as New York, Pennsylvania, and Texas. This is likely an explanation for the relatively low coverage of Asian immigrants reported by SEER [6]. Registries located in areas known to have high concentrations of Asian immigrants must be included in SEER to allow for adequate assessment of the cancer burden in these predominant Asian immigrant groups in the U.S.

In summary, our findings provide evidence for the need to examine Asian subpopulations as individual groups rather than using the aggregate racial/ethnic category known as Asian/PI. True heterogeneity in cancer outcomes exists within these separate groups and requires targeted interventions for specific subpopulations. We have also shed light on the need for individualized interventions for South Asians, particularly for early breast cancer detection. This group has been found to have true histologic differences in their tumors that increase the risk for poor breast cancer prognosis. Despite being a highly educated Asian subpopulation, this group does not seek adequate cancer prevention services, such as breast cancer screening. It is our hope that our findings guide future interventional studies aimed at the South Asian population in the U.S.

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APPENDIX A. Demographic and tumor characteristics of eligible Asian cases with infection-associated cancers prior to sample exclusions

Demographic and tumor characteristics among 1,525 Asian cases diagnosed with primary cervical cancer prior to study sample exclusions

Characteristic	N (%)
Age at diagnosis (years)	
Mean ± SD	54 ± 28
Year of diagnosis	
1999-2001	346 (22.7)
2002-2004	431 (28.3)
2005-2007	431 (28.3)
2008-2009	317 (20.8)
SEER registry	
San Francisco-Oakland	224 (14.7)
Los Angeles	418 (27.4)
San Jose-Monterey	85 (5.6)
Greater California	13 (0.9)
Connecticut	11 (0.7)
Detroit	12 (0.8)
Hawaii	232 (15.2)
Iowa	9 (0.6)
New Mexico	3 (0.2)
Seattle-Puget Sound	75 (4.9)
Utah	5 (0.3)
Atlanta	30 (2.0)
Greater Georgia	298 (19.5)
Rural Georgia	0 (0.0)
Kentucky	1 (0.1)
Louisiana	5 (0.3)
New Jersey	104 (6.8)
Stage at diagnosis	
In situ	0 (0.0)
Early	782 (51.3)
Late	654 (42.9)
Unknown	89 (5.8)
Grade	
I	145 (9.6)
II	415 (27.2)
III	447 (29.3)
IV	41 (2.7)
Unknown	477 (31.3)
Place of birth	
U.S.-born	171 (11.2)
Foreign-born	896 (58.8)
Unknown	458 (30.0)

Demographic and tumor characteristics among 4,051 Asian cases diagnosed with primary hepatocellular carcinoma prior to study sample exclusions

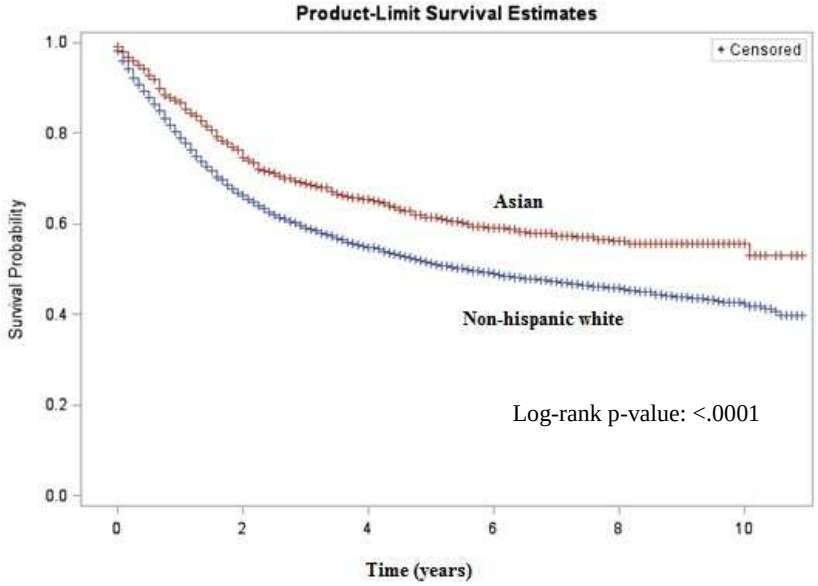
Characteristic	South Asian (n=130)	Chinese (n=1989)	Japanese (n=793)	Filipino (n=1139)
Age at diagnosis (years)				
Mean ± SD	61 ± 12	65 ± 13	70 ± 11	64 ± 13
Sex				
Male	103 (79.2)	1459 (73.4)	384 (48.4)	861 (75.6)
Female	27 (20.8)	530 (26.7)	409 (51.6)	278 (24.4)
Year of diagnosis				
1999-2001	18 (13.9)	433 (21.8)	160 (20.2)	232 (20.4)
2002-2004	35 (26.9)	552 (27.8)	243 (30.6)	293 (25.7)
2005-2007	31 (23.9)	600 (30.2)	220 (27.7)	382 (33.5)
2008-2009	46 (35.4)	404 (20.3)	170 (21.4)	232 (20.4)
SEER registry				
San Francisco-Oakland	9 (6.9)	698 (35.1)	65 (8.2)	220 (19.3)
Los Angeles	7 (5.4)	570 (28.7)	135 (17.0)	283 (24.9)
San Jose-Monterey	3 (2.3)	151 (7.6)	36 (4.5)	71 (6.2)
Greater California	2 (1.5)	6 (0.3)	1 (0.1)	1 (0.1)
Connecticut	5 (3.9)	17 (0.9)	5 (0.6)	7 (0.6)
Detroit	15 (11.5)	21 (1.1)	7 (0.9)	9 (0.8)
Hawaii	0 (0.0)	94 (4.7)	310 (39.1)	150 (13.2)
Iowa	0 (0.0)	4 (0.2)	1 (0.1)	1 (0.1)
New Mexico	2 (1.5)	4 (0.2)	3 (0.4)	1 (0.1)
Seattle-Puget Sound	9 (6.9)	95 (4.8)	52 (6.6)	55 (4.8)
Utah	2 (1.5)	2 (0.1)	8 (1.0)	1 (0.1)
Atlanta	8 (6.2)	14 (0.7)	2 (0.3)	0 (0.0)
Greater Georgia	12 (9.2)	228 (11.5)	158 (19.9)	282 (24.8)
Rural Georgia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Kentucky	1 (0.8)	4 (0.2)	1 (0.1)	0 (0.0)
Louisiana	2 (1.5)	5 (0.3)	1 (0.1)	5 (0.4)
New Jersey	53 (40.8)	76 (3.8)	8 (1.0)	53 (4.7)
Stage at diagnosis				
In situ	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Early	59 (45.4)	1064 (53.5)	448 (56.5)	559 (49.1)
Late	56 (43.1)	560 (28.2)	212 (26.7)	386 (33.9)
Unknown	15 (11.5)	365 (18.4)	133 (16.8)	194 (17.0)
Grade				
I	12 (9.2)	220 (11.1)	115 (14.5)	148 (13.0)
II	22 (16.9)	292 (14.7)	127 (16.0)	188 (16.5)
III	14 (10.8)	175 (8.8)	70 (8.8)	130 (11.4)
IV	2 (1.5)	12 (0.6)	6 (0.8)	12 (1.1)
Unknown	80 (61.5)	1290 (64.9)	475 (59.9)	661 (58.0)
Place of birth				
U.S.-born	4 (3.1)	98 (4.9)	339 (42.8)	97 (8.5)
Foreign-born	80 (61.5)	1398 (70.3)	304 (38.3)	852 (74.8)
Unknown	46 (35.4)	493 (24.8)	150 (18.9)	190 (16.7)

Demographic and tumor characteristics among 4,635 Asian cases diagnosed with primary gastric adenocarcinoma prior to study sample exclusions

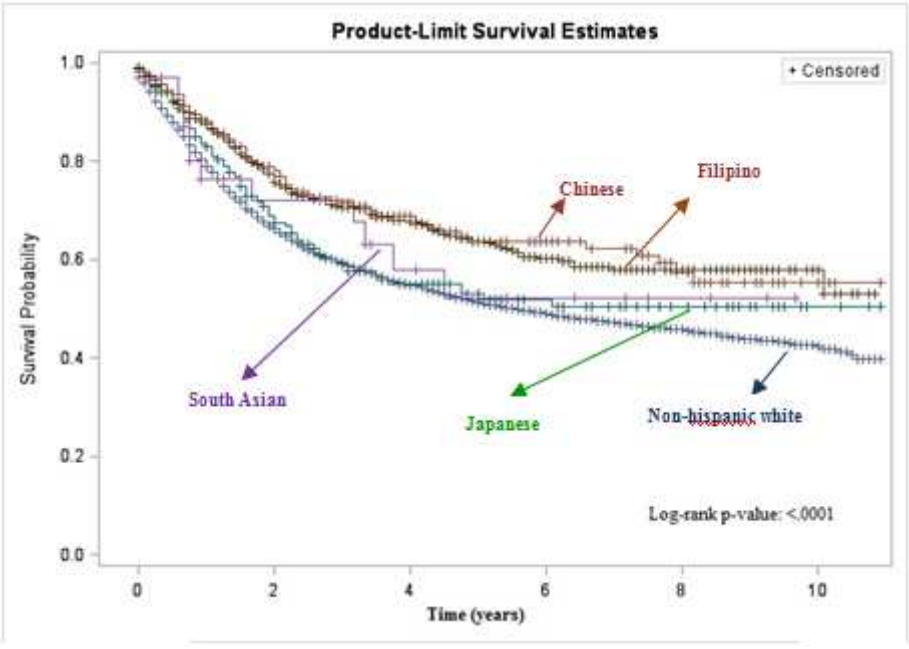
Characteristic	South Asian (n=176)	Chinese (n=1750)	Japanese (n=1874)	Filipino (n=835)
Age at diagnosis (years)				
Mean ± SD	62 ± 16	70 ± 15	75 ± 11	69 ± 14
Sex				
Male	114 (64.8)	1001 (57.2)	1051 (56.1)	447 (53.5)
Female	62 (35.2)	749 (42.8)	823 (43.9)	388 (46.5)
Year of diagnosis				
1999-2001	27 (15.3)	442 (25.3)	562 (30.0)	184 (22.0)
2002-2004	54 (30.7)	475 (27.1)	518 (27.6)	236 (28.3)
2005-2007	54 (30.7)	485 (27.7)	479 (25.6)	247 (29.6)
2008-2009	41 (23.3)	348 (19.9)	315 (16.8)	168 (20.1)
SEER registry				
San Francisco-Oakland	14 (8.0)	553 (31.6)	123 (6.6)	132 (15.8)
Los Angeles	5 (2.8)	536 (30.6)	403 (21.5)	165 (19.8)
San Jose-Monterey	7 (4.0)	146 (8.3)	80 (4.3)	50 (6.0)
Greater California	4 (2.3)	6 (0.3)	7 (0.4)	1 (0.1)
Connecticut	2 (1.1)	14 (0.8)	7 (0.4)	6 (0.7)
Detroit	24 (13.6)	13 (0.7)	5 (0.3)	10 (1.2)
Hawaii	2 (1.1)	97 (5.5)	888 (47.4)	163 (19.5)
Iowa	2 (1.1)	3 (0.2)	4 (0.2)	0 (0.0)
New Mexico	1 (0.6)	2 (0.1)	2 (0.1)	0 (0.0)
Seattle-Puget Sound	8 (4.6)	64 (3.7)	85 (4.5)	41 (4.9)
Utah	2 (1.1)	2 (0.1)	9 (0.5)	1 (0.1)
Atlanta	15 (8.5)	28 (1.6)	9 (0.5)	0 (0.0)
Greater Georgia	9 (5.1)	163 (9.3)	232 (12.4)	220 (26.4)
Rural Georgia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Kentucky	3 (1.7)	4 (0.2)	5 (0.3)	0 (0.0)
Louisiana	1 (0.6)	9 (0.5)	2 (0.1)	3 (0.4)
New Jersey	77 (43.8)	110 (6.3)	13 (0.7)	43 (5.2)
Stage at diagnosis				
In situ	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Early	45 (25.6)	574 (32.8)	687 (36.7)	257 (30.8)
Late	106 (60.2)	929 (53.1)	972 (51.9)	477 (57.1)
Unknown	25 (14.2)	247 (14.1)	215 (11.5)	101 (12.1)
Grade				
I	8 (4.6)	45 (2.6)	78 (4.2)	19 (2.3)
II	40 (22.7)	354 (20.2)	436 (23.3)	169 (20.2)
III	101 (57.4)	1071 (61.2)	1114 (59.5)	509 (61.0)
IV	1 (0.6)	35 (2.0)	28 (1.5)	10 (1.2)
Unknown	26 (14.8)	245 (14.0)	218 (11.6)	128 (15.3)
Place of birth				
U.S.-born	8 (4.6)	86 (4.9)	1053 (56.2)	85 (10.2)
Foreign-born	113 (64.2)	1087 (62.1)	450 (24.0)	572 (68.5)
Unknown	55 (31.3)	577 (33.0)	371 (19.8)	178 (21.3)

APPENDIX B. Unadjusted Kaplan-Meier curves of overall survival among cases diagnosed with infection-associated cancers

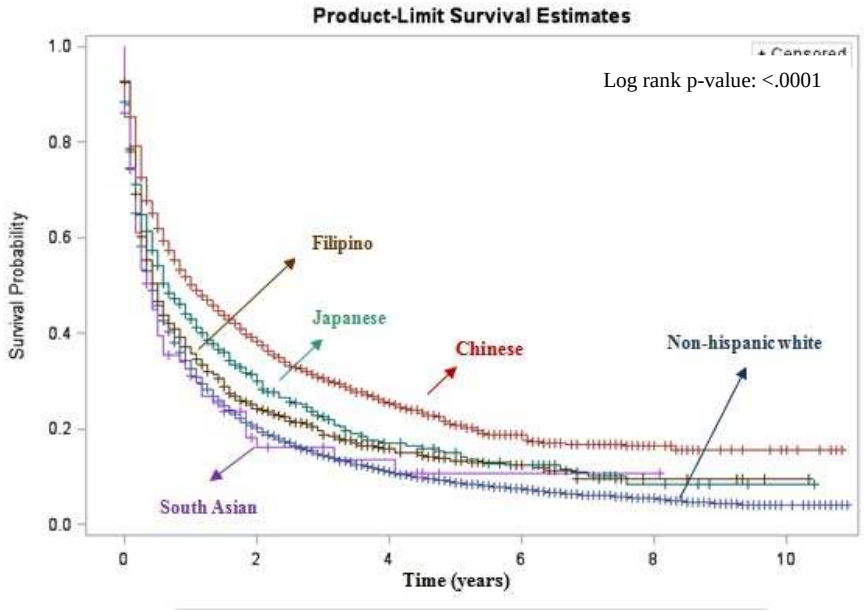
Unadjusted Kaplan-Meier curves of overall cervical cancer survival comparing Asians to non-Hispanic whites



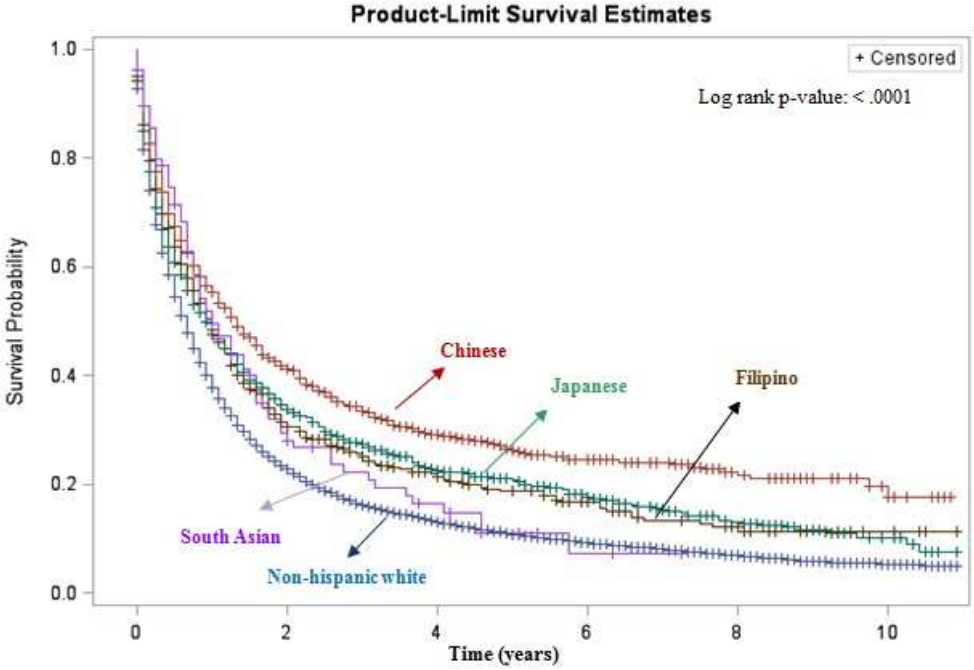
Unadjusted Kaplan-Meier curves of overall cervical cancer survival comparing South Asians to other Asian subgroups and non-Hispanic whites



Unadjusted Kaplan-Meier curves of overall liver cancer survival comparing South Asians to other Asian subgroups and non-Hispanic whites



Unadjusted Kaplan-Meier curves of overall stomach cancer survival comparing South Asians to other Asian subgroups and non-Hispanic whites



APPENDIX C. Demographic and tumor characteristics of eligible Asian cases with breast cancer prior to sample exclusions

Demographic and tumor characteristics among 31,572 Asian women diagnosed with primary breast cancer prior to study sample exclusions

Characteristic	South Asian (n=2054)	Chinese (n=9186)	Japanese (n=8076)	Filipino (n=12256)
Age at diagnosis, y				
Mean ± SD	54 ± 12	57 ± 14	63 ± 17	57 ± 12
Year of diagnosis				
1999-2001	381 (18.6)	1978 (21.5)	2161 (26.8)	2514 (20.5)
2002-2004	502 (24.4)	2397 (26.1)	2255 (27.9)	3200 (26.1)
2005-2007	622 (30.2)	2662 (29.0)	2089 (25.9)	3724 (30.4)
2008-2009	549 (26.7)	2149 (23.4)	1571 (19.5)	2818 (23.0)
SEER Registry				
San Francisco-Oakland	130 (6.3)	2926 (31.9)	558 (6.9)	2022 (16.5)
Los Angeles	69 (3.4)	2281 (24.8)	1511 (18.7)	3270 (26.7)
San Jose-Monterey	120 (5.8)	810 (8.8)	400 (5.0)	642 (5.2)
Greater California	84 (4.1)	21 (0.2)	21 (0.3)	36 (0.3)
Connecticut	138 (6.7)	80 (0.9)	23 (0.3)	63 (0.5)
Detroit	149 (7.3)	82 (0.9)	31 (0.4)	69 (0.6)
Hawaii	5 (0.2)	799 (8.7)	3916 (48.5)	1517 (12.4)
Iowa	9 (0.4)	19 (0.2)	6 (0.1)	11 (0.1)
New Mexico	15 (0.7)	6 (0.1)	13 (0.2)	11 (0.1)
Seattle-Puget Sound	115 (5.6)	358 (3.9)	389 (4.8)	551 (4.5)
Utah	13 (0.6)	21 (0.2)	60 (0.7)	11 (0.1)
Atlanta	171 (8.3)	98 (1.1)	21 (0.3)	16 (0.1)
Greater Georgia	149 (7.3)	1065 (11.6)	994 (12.3)	3146 (25.7)
Rural Georgia	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Kentucky	19 (0.9)	8 (0.1)	16 (0.2)	14 (0.1)
Louisiana	31 (1.5)	24 (0.3)	13 (0.2)	17 (0.1)
New Jersey	836 (40.7)	588 (6.4)	104 (1.3)	860 (7.0)
Stage at diagnosis				
In situ	416 (20.3)	2319 (25.2)	1998 (24.7)	2843 (23.2)
I	616 (30.0)	3217 (35.0)	3360 (41.6)	3951 (32.2)
II	626 (30.5)	2453 (26.7)	1930 (23.9)	3602 (29.4)
III	213 (10.4)	570 (6.2)	367 (4.5)	986 (8.0)
IV	78 (3.8)	220 (2.4)	183 (2.3)	446 (3.6)
Unknown	105 (5.1)	407 (4.4)	238 (2.9)	428 (3.5)
Grade				
I	252 (12.3)	1437 (15.6)	1906 (23.6)	1651 (13.5)
II	668 (32.5)	3520 (38.3)	3273 (40.5)	4685 (38.2)
III	800 (39.0)	2751 (30.0)	1956 (24.2)	4023 (32.8)
IV	48 (2.3)	466 (5.1)	277 (3.4)	613 (5.0)
Unknown	286 (13.9)	1012 (11.0)	664 (8.2)	1284 (10.5)

ER Status				
Positive/borderline	1232 (60.0)	5734 (62.4)	5421 (67.1)	7743 (63.2)
Negative	414 (20.2)	1468 (16.0)	1041 (12.9)	2135 (17.4)
Unknown	408 (19.9)	1984 (21.6)	1614 (20.0)	2378 (19.4)
PR Status				
Positive/borderline	1059 (51.6)	4884 (53.2)	4619 (57.2)	6337 (51.7)
Negative	564 (27.5)	2172 (23.6)	1679 (20.8)	3190 (26.0)
Unknown	431 (21.0)	2130 (23.2)	1778 (22.0)	2729 (22.3)
Place of birth				
U.S.-born	117 (5.7)	932 (10.2)	3639 (45.1)	711 (5.8)
Foreign-born	892 (43.4)	4629 (50.4)	1519 (18.8)	7993 (65.2)
Unknown	1045 (50.9)	3625 (39.5)	2918 (36.1)	3552 (29.0)

APPENDIX D. Demographic and tumor characteristics of eligible Asian Medicare beneficiaries with breast cancer prior to sample exclusions

Demographic and tumor characteristics among 13,293 Asian female Medicare beneficiaries diagnosed with invasive breast cancer in SEER-Medicare prior to study sample exclusions

Characteristic	N (%)
Age at diagnosis, y	
Mean ± SD	68 ± 10
Year of diagnosis	
1999-2001	3715 (28.0)
2002-2004	3753 (28.2)
2005-2007	3522 (26.5)
2008-2009	2303 (17.3)
Income (of census tract)	
Quartile 1	2230 (16.8)
Quartile 2	2680 (20.2)
Quartile 3	3928 (30.0)
Quartile 4	4408 (33.2)
Unknown	47 (0.4)
Education (% <HS in census tract)	
Quartile 1	2895 (21.8)
Quartile 2	3334 (25.1)
Quartile 3	3473 (26.1)
Quartile 4	3544 (26.7)
Unknown	47 (0.4)
Place of birth	
U.S.-born	2850 (21.4)
Foreign-born	5893 (44.3)
Unknown	4550 (34.2)
Stage at diagnosis	
In situ	2850 (21.4)
Early	8638 (65.0)
Late	1233 (9.3)
Unknown	572 (4.3)
Grade at diagnosis	
I	2531 (19.0)
II	5317 (40.0)
III	3472 (26.1)
IV	520 (3.9)
Unknown	1453 (10.9)
ER Status	
Positive/borderline	8366 (62.9)
Negative	1897 (14.3)
Unknown	3030 (22.8)

PR Status	6859 (51.6)
Positive/borderline	3108 (23.4)
Negative	3326 (25.0)
Unknown	

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Publications and Conference Presentations

George N, Welles SL, Liu L, Robinson LF, DeRoos AJ, Evans AA. Breast cancer stage at diagnosis and stage-specific survival among South Asians and other Asian subpopulations in the United States. *(In progress)*

Yang HP, Murphy KR, Pfeiffer RM, **George N**, Garcia-Closas M, Lissowska J, Brinton La, Wentzensen N. Lifetime ovulatory cycles and risk of ovarian and endometrial cancers. *(In progress)*

Yang HP, Murphy K, **George N**, Garcia-Closas M, Lissowska J, Brinton LA, Wentzensen N. Lifetime ovulatory cycles and risk of ovarian and endometrial cancers. Poster presentation at American Association for Cancer Research Annual Meeting, April 7, 2013, Washington DC